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Dated this 18th day of August, 2006

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[Item] Specification 1

[Item] Abstract 1

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[Name of Document] Specification

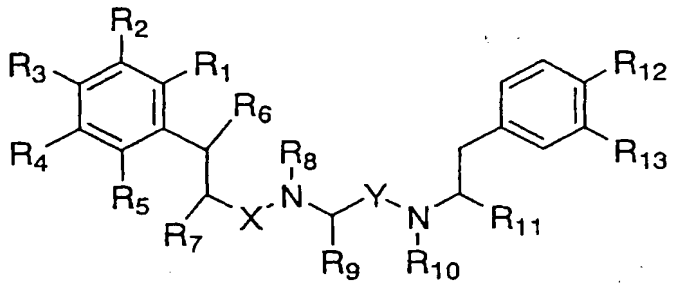
[Title of the Invention]

HALOGEN-SUBSTITUTED BENZENE DERIVATIVES

[Claims]

[Claim 1] A compound of Formula (1):

[Chemical Formula 1]



(1)

wherein:

R_1, R_2, R_3, R_4 and R_5 are hydrogen, halogen, hydroxy or amino and at least one of R_1, R_2, R_3, R_4 and R_5 is halogen;

R_6 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, amino or hydroxy;

R_7 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, optionally substituted amino or hydroxy;

R_8 is hydrogen, methyl or ethyl;

R_9 is optionally substituted straight-chained or branched C_{1-6}alkyl, C_{3-7}cycloalkyl or optionally substituted phenyl;

R_{10} is hydrogen, methyl or ethyl;

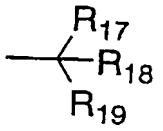
R_{11} is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, -CO-N(R_{14})R_{15} or an optionally

substituted heterocyclic ring;

R_{12} is hydroxy or $-OR_{16}$;

R_{13} is hydrogen, straight-chained or branched C_{1-6}alkyl, straight-chained or branched C_{2-6}alkenyl, straight-chained or branched C_{2-6}alkynyl or a group of Formula (2):

[Chemical Formula 2]



(2)

R_{14} and R_{15}, which may be the same or different, are hydrogen, optionally substituted straight-chained or branched C_{1-4}alkyl, C_{3-7}cycloalkyl, straight-chained or branched C_{1-4}alkyloxy, straight-chained or branched C_{1-4}alkylsulfonyl or a heterocyclic ring, or R_{14} and R_{15}, as $-N(R_{14})R_{15}$, form optionally substituted 3- to 7-membered cyclic amine;

R_{16} is straight-chained C_{1-4}alkyl;

R_{17} is hydrogen or methyl;

R_{18} and R_{19} together form C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl;

X is carbonyl or methylene;

Y is carbonyl or methylene;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 2] The compound according to claim 1, wherein in Formula (1) at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are hydrogen or hydroxy;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 3] The compound according to claim 1, wherein in Formula (1) R_3 is halogen or R_2 and R_3 are the same kind of halogen;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 4] The compound according to claim 1, wherein in Formula (1) R_3 is halogen and R_1, R_2, R_4 and R_5 are hydrogen, or R_2 and R_3 are the same kind of halogen and R_1, R_4 and R_5 are hydrogen;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 5] The compound according to any one of claims 1-4, wherein R_6 in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 6] The compound according to any one of claims 1-5, wherein R_7 in Formula (1) is hydrogen or optionally substituted amino;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 7] The compound according to any one of claims 1-6, wherein R_8 in Formula (1) is hydrogen or methyl;
or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 8] The compound according to any one of claims 1-7, wherein R_9 in Formula (1) is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, cyclohexyl, phenyl, benzyl, para-

hydroxybenzyl or cyclohexylmethyl;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 9] The compound according to any one of claims 1-8,

wherein R_{10} in Formula (1) is hydrogen or methyl;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 10] The compound according to any one of claims 1-9,

wherein R_{11} in Formula (1) is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, ethylcarbamoyl, 2-pyridylcarbamoyl, methoxycarbamoyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl or 6-methyl-4-pyrimidinon-2-yl, methylcarbamoyl;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 11] The compound according to any one of claims 1-10,

wherein R_{12} in Formula (1) is hydroxy;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 12] The compound according to any one of claims 1-11,

wherein R_{13} in Formula (1) is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 13] The compound according to claim 1,

wherein in Formula (1)

at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the

others are hydrogen or hydroxy;

R_6 is hydrogen or methyl;

R_7 is hydrogen or optionally substituted amino;

R_8 is hydrogen or methyl;

R_9 is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3,-hexafluoro-2-propyl, cyclohexyl, phenyl, benzyl, phenethyl, para-hydroxybenzyl or cyclohexylmethyl;

R_{10} is hydrogen or methyl;

R_{11} is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, ethylcarbamoyl, 2-pyridylcarbamoyl, methoxycarbamoyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl or 6-methyl-4-pyrimidinon-2-yl;

R_{12} is hydroxy;

R_{13} is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 14] The compound according to claim 1 which is selected from the group of compounds consisting of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide, N-(2-(2-((2-amino-3-(4-

fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea, N-(2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tertbutyl-4-hydroxyphenyl)propyl)sulfamide, N-[2-(3-tertbutyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalanyloyl)methylamino]-3-methylbutanamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide, 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol, 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide and 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-

triazol-2-yl)ethylamide;

or a hydrate or pharmaceutically acceptable salt thereof.

[Claim 15] A medicine containing the compound according to any one of claims 1-14 as an active ingredient

[Claim 16] A motilin receptor antagonist containing the compound according to any one of claims 1-14.

[Claim 17] A gastrointestinal motility suppressor agent containing the compound according to any one of claims 1-14 as an active ingredient

[Claim 18] A therapeutic of hypermotilinemia containing the compound according to any one of claims 1-14 as an active ingredient.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

This invention relates to halogen-substituted benzene derivatives that function as a motilin receptor antagonist and that are useful as medicines.

[0002]

[Prior Art]

Motilin, which is one of the gastrointestinal hormones, is a straight-chained peptide consisting of 22 amino acids and is well known to be responsible for regulating the motility of the gastrointestinal tract in animals including human. It has been reported that exogenously administered motilin causes contractions in humans and dogs that are similar to interdigestive

migrating contractions, thus promoting gastric emptying (Itoh et al., Scand. J. Gastroenterol., 11, 93-110 (1976); Peeters et al., Gastroenterology 102, 97-101 (1992)). Hence, erythromycin derivatives which are an agonist of motilin are under development as an gastrointestinal tract motor activity enhancer (Satoh et al., J. Pharmacol. Exp. Therap., 271, 574-579 (1994); Lartey et al., J. Med. Chem., 38, 1793-1798 (1995); Drug of the Future, 19, 910-912 (1994)).

[0003]

Peptide and polypeptide derivatives have been reported as antagonists of motilin receptors (Depoortere et al., Eur. J. Pharmacol., 286, 241-247 (1995); Poitras et al., Biochem. Biophys. Res. Commun., 205, 449-454 (1994); Takanashi et al., J. Pharmacol. Exp. Ther., 273, 624-628 (1995)). These derivatives are used as a pharmacological tool in the study of the action of motilin on the motility of the gastrointestinal tract and in the research and development of medicines in the field of the art contemplated by the invention.

[0004]

Motilin receptors had been known to occur principally in the duodenum but recently it has been shown that they also occur in the large intestine, or the lower part of the gastrointestinal tract (William et al., Am. J. Physiol., 262, G50-G55 (1992)), and this indicates the possibility that motilin is involved not only in the motility of the upper part of the gastrointestinal tract but also in the motility of its lower part.

[0005]

Reports have also been made of the cases of hypermotilinemia in patients with irritable bowel syndrome who were manifesting diarrhea and in patients with irritable bowel syndrome who were under stress (Preston et al., Gut, 26, 1059-1064 (1985); Fukudo et al., Tohoku J. Exp. Med., 151, 373-385 (1987)) and this suggests the possibility that increased blood motilin levels are involved in the disease. Other diseases that have been reported to involve hypermotilinemia include crohn's disease, ulcerative colitis, pancreatitis, diabetes mellitus, obesity, malabsorption syndrome, bacterial diarrhea, atrophic gastritis and postgastroenterectomy syndrome. The antagonists of motilin receptors have the potential to ameliorate irritable bowel syndrome and other diseased states accompanied by increased blood motilin levels.

[0006]

[Problems to be Solved by the Invention]

An object of the present invention is to provide halogen-substituted benzene derivatives that function as an antagonist of motilin receptors and which are useful as medicines.

[0007]

[Means for Solving the Problems]

The present inventors conducted repeated intensive studies in an attempt to develop compounds having an outstanding motilin receptor antagonistic action. As a

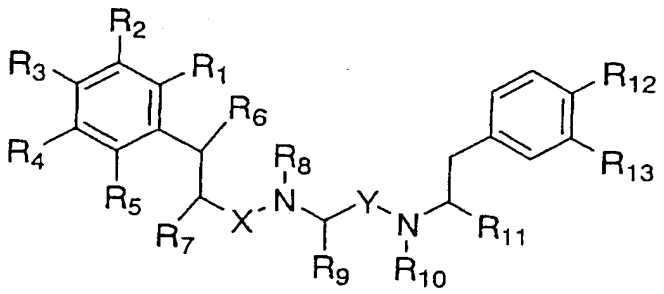
result, they found that substituted phenethylamine derivatives represented by Formula (1) were an excellent antagonist of motilin receptors. The present invention has been accomplished on the basis of this finding.

[0008]

Thus, the present invention provides compounds of Formula (1):

[0009]

[Chemical Formula 3]



(1)

[0010]

wherein:

R_1, R_2, R_3, R_4 and R_5 are hydrogen, halogen, hydroxy or amino and at least one of R_1, R_2, R_3, R_4 and R_5 is halogen;

[0011]

R_6 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, amino or hydroxy;

[0012]

R_7 is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, optionally substituted amino or hydroxy;

[0013]

R_8 is hydrogen, methyl or ethyl;

[0014]

R_9 is optionally substituted straight-chained or branched C_{1-6}alkyl, C_{3-7}cycloalkyl or optionally substituted phenyl;

[0015]

R_{10} is hydrogen, methyl or ethyl;

[0016]

R_{11} is hydrogen, optionally substituted straight-chained or branched C_{1-3}alkyl, $-CO-N(R_{14})R_{15}$ or an optionally substituted heterocyclic ring;

[0017]

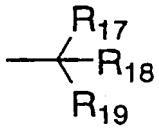
R_{12} is hydroxy or $-OR_{16}$;

[0018]

R_{13} is hydrogen, straight-chained or branched C_{1-6}alkyl, straight-chained or branched C_{2-6}alkenyl, straight-chained or branched C_{2-6}alkynyl or a group of Formula (2):

[0019]

[Chemical Formula 4]



(2)

[0020]

[0021]

R_{14} and R_{15}, which may be the same or different, are hydrogen, optionally substituted straight-chained or branched C_{1-4}alkyl, C_{3-7}cycloalkyl, straight-chained or branched C_{1-4}alkyloxy, straight-chained or branched C_{1-4}alkylsulfonyl or a heterocyclic ring, or R_{14} and R_{15}, as

$-N(R_{14})R_{15}$, form optionally substituted 3- to 7-membered cyclic amine;

[0022]

R_{16} is straight-chained C_{1-4}alkyl;

[0023]

R_{17} is hydrogen or methyl;

[0024]

R_{18} and R_{19} together form C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl;

[0025]

X is carbonyl or methylene;

[0026]

Y is carbonyl or methylene;

or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides a medicine containing a compound of Formula (1) as an active ingredient. Further, the present invention provides a motilin receptor antagonist composition containing the compound. The present invention also provides a gastrointestinal motility suppressor agent containing the compound as an active ingredient. Further, the present invention provides a therapeutic of hypermotilinemia containing the compound as an active ingredient.

[0027]

In the definition of the compounds of Formula (1), halogen as R_1, R_2, R_3, R_4 and R_5 is preferably fluorine or chlorine, with fluorine being more preferred. When at least 2 of R_1 to R_5 are halogen, they may be the same or different

halogen, however it is preferable that they are the same. The number of halogen atoms is preferably 1 to 3 and more preferably 1 or 2.

[0028]

Preferably, at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are independently hydrogen or hydroxy. Preferably, R_3 is halogen or R_2 and R_3 are the same kind of halogen.

[0029]

Preferred compounds include those in which R_3 is halogen and R_1, R_2, R_4 and R_5 are hydrogen; or those in which R_2 and R_3 are the same halogen and R_1, R_4 and R_5 are hydrogen.

[0030]

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 is preferably methyl or ethyl.

[0031]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 include halogen, with fluorine being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

[0032]

The optionally substituted straight-chained or branched C_{1-3}alkyl as R_6 is preferably methyl, ethyl, fluoromethyl or trifluoromethyl, with methyl being particularly preferred.

[0033]

While R_6 has the definitions set forth above, R_6 is preferably hydrogen or methyl.

[0034]

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_7 is preferably methyl.

[0035]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_7 include halogen, with fluorine being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

[0036]

The optionally substituted straight-chained or branched C_{1-3}alkyl as R_7 is preferably methyl or trifluoromethyl, with methyl being particularly preferred.

[0037]

Exemplary substituents of the optionally substituted amino as R_7 include straight-chained or branched C_{1-3}alkyl, with methyl and ethyl being preferred. The amino may have one or more of the above-mentioned substituents, which may be the same or different.

[0038]

The optionally substituted amino as R_7 is preferably amino optionally substituted with one or more of the same or different kinds of straight-chained or branched C_{1-3}alkyl; specific examples include amino, methylamino, dimethylamino and ethylamino, with amino and methylamino being particularly preferred.

[0039]

While R_7 has the definitions set forth above, R_7 is preferably hydrogen or optionally substituted amino, with hydrogen, amino and methylamino being particularly preferred.

[0040]

R_8 is preferably hydrogen or methyl.

[0041]

The alkyl of the optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 is preferably straight-chained or branched C_{1-5}alkyl, e.g., methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl and neopentyl.

[0042]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 include substituted or unsubstituted phenyl (e.g., phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl), C_{3-7}cycloalkyl, and halogen (particularly fluorine).

[0043]

The optionally substituted straight-chained or branched C_{1-6}alkyl as R_9 is preferably methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, benzyl, para-hydroxybenzyl, phenethyl or cyclohexylmethyl.

[0044]

The C_{3-7}cycloalkyl as R_9 is preferably cyclopentyl or cyclohexyl.

[0045]

Exemplary substituents of the optionally substituted phenyl as R_9 include hydroxy, amino, methyl, ethyl and halogen. The phenyl may have one or more of the above-mentioned substituents, which may be the same or different.

[0046]

The optionally substituted phenyl as R_9 is preferably phenyl.

[0047]

While R_9 has the definitions set forth above, R_9 is preferably methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, cyclohexyl, phenyl, benzyl, para-hydroxybenzyl, phenethyl or cyclohexylmethyl.

[0048]

R_{10} is preferably hydrogen or methyl.

[0049]

The alkyl of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} is preferably methyl.

[0050]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} include amino optionally substituted with one or more of the same or different kind of straight-chained or branched C_{1-3}alkyl (e.g., amino, methylamino, dimethylamino and ethylamino), optionally substituted 3- to 7-membered cyclic amino (exemplary substituents of the cyclic amino include hydroxy, amino, carboxyl, carbamoyl and methyl), hydroxy, methoxy, halogen, carbamoyl, methanesulfonyl, ureide, guanidyl,

N'-cyano-N"-methylguanidyl, sulfamoylamino, carbamoylmethylamino and methanesulfonylamino, with amino, hydroxy, carbamoyl, methanesulfonyl, ureide, sulfamoylamino, methanesulfonylamino and carbamoylmethylamino being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

[0051]

The optionally substituted straight-chained or branched C_{1-3}alkyl as R_{11} is preferably methyl, aminomethyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, guanidylmethyl, sulfamoylaminomethyl or methanesulfonylaminomethyl, with methyl, hydroxymethyl and methanesulfonylmethyl being more preferred.

[0052]

The alkyl of the optionally substituted straight-chained or branched C_{1-4}alkyl as R_{14} and R_{15} of $-CO-N(R_{14})R_{15}$ as R_{11} is preferably methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl or tert-butyl, with methyl being more preferred.

[0053]

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-4}alkyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} include optionally substituted straight-chained or branched C_{1-3}alkoxy (exemplary substituents of the optionally substituted straight-chained or branched C_{1-3}alkoxy include hydroxy, amino, carboxyl and carbamoyl), hydroxy, amino, methylamino, dimethylamino, carbamoyl and methanesulfonyl, with hydroxy, methoxy and methanesulfonyl being preferred.

[0054]

Examples of the optionally substituted straight-chained or branched C_{1-4}alkyl as R_{14} and R_{15} in -CO-N(R_{14})R_{15} as R_{11} include methyl, ethyl, tert-butyl, hydroxymethyl, methoxymethyl, 2-hydroxyethyl, 2-aminoethyl, 2-hydroxy-2-methylpropyl, 2-hydroxy-2-methylpropyl, 2-amino-2-methylpropyl and methanesulfonylmethyl, with methyl, ethyl, tert-butyl, hydroxymethyl, methoxymethyl and methanesulfonylmethyl being preferred.

[0055]

The C_{3-7}cycloalkyl as R_{14} and R_{15} in -CO-N(R_{14})R_{15} as R_{11} is preferably cyclopropyl.

[0056]

The straight-chained or branched C_{1-4}alkyloxy as R_{14} and R_{15} in -CO-N(R_{14})R_{15} as R_{11} is preferably methoxy.

[0057]

The straight-chained or branched C_{1-4}alkylsulfonyl as R_{14} and R_{15} in -CO-N(R_{14})R_{15} as R_{11} is preferably methanesulfonyl.

[0058]

Examples of the heterocyclic ring as R_{14} and R_{15} in -CO-N(R_{14})R_{15} as R_{11} include aliphatic or aromatic 5- or 6-membered rings containing at least one hetero atom selected from among N, S and O; specific examples include 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazinyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl and triazolyl, with 2-pyridyl being preferred.

[0059]

The 3- to 7-membered cyclic amine of the optionally substituted 3- to 7-membered cyclic amine as $-N(R_{14})R_{15}$ as R_{11} include aziridine, azetidine, pyrrolidine, piperidine, piperazine and morpholine, with piperazine and morpholine being preferred. Exemplary substituents of the optionally substituted 3- to 7-membered cyclic amine include hydroxy, amino, carboxyl, carbamoyl and methyl.

[0060]

The $-CO-N(R_{14})R_{15}$ as R_{11} is preferably carbamoyl, methylcarbamoyl, ethylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, hydroxymethylcarbamoyl or methoxymethylcarbamoyl, with carbamoyl, ethylcarbamoyl and 2-pyridylcarbamoyl being more preferred.

[0061]

Examples of the heterocyclic ring of the optionally substituted heterocyclic ring as R_{11} include aliphatic or aromatic 5- or 6-membered rings containing at least one hetero atom selected from among N, S and O. Exemplary substituents of the heterocyclic ring include oxo, hydroxy, methyl, ethyl and trifluoromethyl; the heterocyclic ring may have one or more of the above-mentioned substituents, which may be the same or different. Specific examples of the optionally substituted heterocyclic ring include furyl, thienyl, pyrrolyl, oxazolyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-triazol-2-yl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 4-pyrimidinon-2-yl, 6-methyl-4-pyrimidinon-2-yl

and imidazolidine-2,4-dion-5-yl, with 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl and 6-methyl-4-pyrimidino-2-yl being preferred.

[0062]

While R_{11} has the definitions set forth above, R_{11} is preferably methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, ethylcarbamoyl, 2-pyridylcarbamoyl, methoxycarbamoyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl and 6-methyl-4-pyrimidinon-2-yl, with carbamoyl and ethylcarbamoyl being more preferred.

[0063]

The straight-chained C_{1-4}alkyl as R_{16} of $-OR_{16}$ as R_{12} is preferably methyl.

[0064]

R_{12} is preferably hydroxy.

[0065]

The straight-chained or branched C_{1-6}alkyl as R_{13} is preferably straight-chained or branched C_{2-5}alkyl, more preferably branched C_{3-5}alkyl, and most preferably tert-butyl.

[0066]

The straight-chained or branched C_{2-6}alkenyl as R_{13} is preferably straight-chained or branched C_{3-5}alkenyl and more preferably branched C_{3-5}alkenyl.

[0067]

The straight-chained or branched C_{2-6}alkynyl as R_{13} is preferably straight-chained or branched C_{3-5}alkynyl and more

preferably branched C_{3-5}alkynyl.

[0068]

R_{17} in Formula (3) as R_{13} is preferably methyl.

[0069]

The C_{3-7}cycloalkyl formed by R_{18} and R_{19} in Formula (2) as R_{13} is preferably C_{3-5}cycloalkyl.

[0070]

The C_{3-7} cycloalkenyl formed by R_{18} and R_{19} in Formula (2) as R_{13} is preferably C_{3-5}cycloalkenyl.

[0071]

While R_{13} has the definitions set forth above, R_{13} is preferably isopropyl, tert-butyl, 1,1-dimethylpropyl and 1,1-dimethyl-2-propenyl, with tert-butyl being more preferred.

[0072]

X is preferably carbonyl or methylene.

[0073]

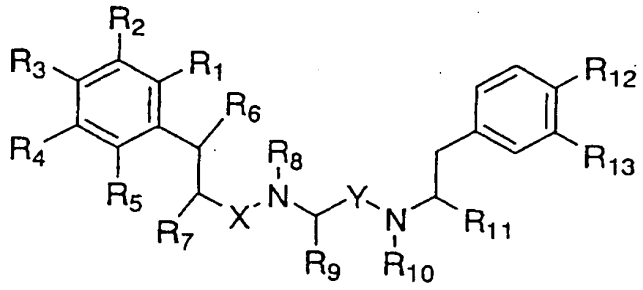
Y is preferably carbonyl or methylene.

[0074]

Examples of compounds of Formula (1)

[0075]

[Chemical Formula 5]



(1)

[0076]

wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, X and Y are as defined as above

include those compounds in which at least one of R_1, R_2, R_3, R_4 and R_5 is halogen and the others are hydrogen or hydroxy; R_6 is hydrogen or methyl; R_7 is hydrogen or optionally substituted amino; R_8 is hydrogen or methyl; R_9 is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, 1,1,1,3,3,3-hexafluoro-2-propyl, cyclohexyl, phenyl, benzyl, phenethyl, para-hydroxybenzyl or cyclohexylmethyl; R_{10} is hydrogen or methyl; R_{11} is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, ethylcarbamoyl, 2-pyridylcarbamoyl, methoxycarbamoyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl or 6-methyl-4-pyrimidinon-2-yl; R_{12} is hydroxy; R_{13} is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl. More preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide, N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea,

N-(2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propyl)sulfamide, N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalanynoyl)methylamino]-3-methylbutanamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide, 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol, 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide and 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide. Particularly preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2, Phe(4-Cl)-N-Me-Val-N-Me-

Tyr(3-tBu)-NH_2, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide and 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol.

[0077]

Salt-forming acids include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, tartaric acid, methanesulfonic acid and trifluoroacetic acid.

[0078]

The compounds of the present invention can occur as optical isomers and the respective optical isomers and mixtures thereof are all included within the scope of the invention.

[0079]

The compounds of the present invention can also be obtained as hydrates.

[0080]

On the pages that follow, the present invention is described more specifically and the amino acids that constitute peptides, the amino acids protected by protecting groups, the protecting groups and reagents are

represented by the following abbreviations:

Val: valine, Phe: phenylalanine, Tyr: tyrosine, Z: benzyloxycarbonyl, Boc: tert-butoxycarbonyl, CMPI: 2-chloro-1-methylpyridinium iodide, PyCIU: chloro-N,N,N',N'-bis(tetramethylene)formamidinium hexafluorophosphate, DIC: N,N'-diisopropylcarbodiimide, HOBT: 1-hydroxylbenzotriazole monohydrate, NMM: N-methylmorpholine, TEA: triethylamine, DIEA: diisopropylethylamine, TFA: trifluoroacetic acid, THF: tetrahydrofuran, and DMF: N,N-dimethylformamide.

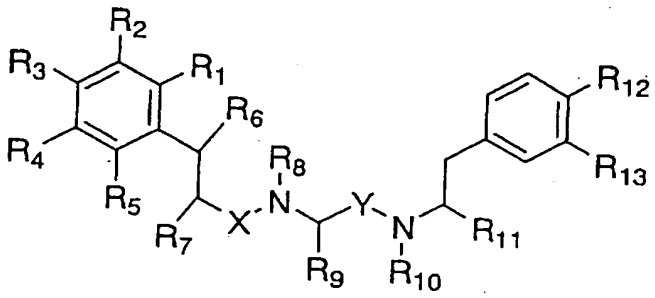
[0081]

[Mode for Carrying Out the Invention]

The compounds of Formula (1)

[0082]

[Chemical Formula 6]



(1)

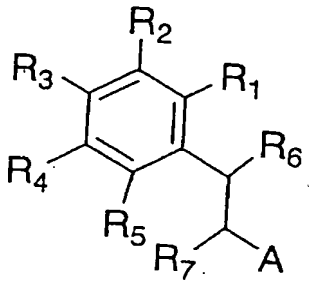
[0083]

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, X and Y are as defined above

can basically be produced by binding Compound (I), Compound (II) and Compound (III), which are represented by the following formulae and in which functional groups other than those involved in bond formation are protected as required:

[0084]

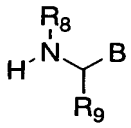
[Chemical Formula 7]



(I)

[0085]

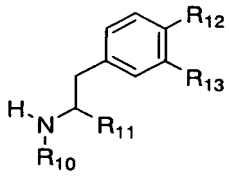
[Chemical Formula 8]



(II)

[0086]

[Chemical formula 9]



(III)

[0087]

A and B in Formulae (I) to (III) are functional groups which can form a bond by the reaction with amino; specific examples are carboxyl, formyl, halomethylene of which halogen is chlorine, bromine or iodine, and sulfonyloxymethylene of which sulfonyl is methanesulfonyl, trifluoromethanesulfonyl, paratoluenesulfonyl and the like. R_1 to R_{10}, R_{12} and R_{13} are as defined above, provided that when they are reactive groups such as amino, hydroxy or

carboxyl, they are protected by normally used appropriate protecting groups, if desired. R_{11} is as defined above or is a functional group which is convertible to one of the above defined groups.

[0088]

The compounds of Formula (1) may be produced by first binding Compound (II) and Compound (III), optionally followed by deprotection, and then binding the resultant compound with Compound (I), optionally followed by deprotection or conversion of the functional group(s). Alternatively, the compound of Formula (1) may be produced by first binding Compound (I) and Compound (II), optionally followed by deprotection, and then binding the resultant compound with Compound (III), optionally followed by deprotection or conversion of the functional group(s).

[0089]

The compounds of the present invention may be produced by either the solid-phase process or the liquid-phase process. In the production by the solid-phase process, an automatic organic synthesizer can be used but it may be replaced by the manual procedure.

[0090]

Almost all amino acids that are used for the production of the compounds of the present invention are commercially available and readily purchasable. Those which are not commercially available can be produced by well-known established methods such as the Strecker synthesis, the Bucherer method, the acetamido malonic ester method,

the method of alkylating an amino group protected glycine ester and the Z-α-phosphonoglycine trimethylester method.

[0091]

Compound (I), if it has a functional group such as amino and hydroxy, with the functional group being protected, is carboxylic acid (A is $-CO_2H$), aldehyde (A is -CHO), alkylhalide (A is $-CH_2$-Hal), sulfonate (A is $-CH_2-OSO_2R$) or the like. In this case, bond can be formed by reacting A of Compound (I) with the amino group of Compound (II).

[0092]

Compound (II) can, in almost all cases, be derived from an α-amino acid and B is carboxyl ($-CO_2H$), formyl (-CHO), halomethyl ($-CH_2$-Hal), sulfonyloxymethyl (RSO_2O-CH_2-) or the like. The amino group of Compound (II) is reacted with A of Compound (I) to form bond and B of Compound (II) is reacted with the amino group of Compound (III) to form bond.

[0093]

Compound (III) is an ethylamine derivative and can be generally derived from an amino acid. The amino group of Compound (III) is reacted with B of Compound (II) to form bond.

[0094]

When A or B is carboxyl, various methods known in peptide synthesis may be used to activate the carboxyl for condensation with the amino group and such methods include the use of benzotriazol-1-yl-oxy-

tris(dimethylamino)phosphonium hexafluorophosphate (BOP), the use of PyCIU, the use of bromo tripyrrolidino phosphonium hexafluorophosphate (PyBrop), the use of chlorotripyrrolidino phosphonium hexafluorophosphate (PyClop), the use of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), the use of DIC, the use of N-ethyl-N'-3-dimethylaminopropyl carbodiimide (WSCI), the use of dicyclohexyl carbodiimide (DCC), the use of diphenylphosphorylazide (DPPA), the use of CMPI, the use of 2-bromo-1-methylpyridinium iodide (BMPI), the combination of one of these reagents with HOBT or N-hydroxysuccinimide (HONSu), the mixed acid anhydride method using isobutyl chloroformate or the like, the method of changing the carboxyl group to a pentafluorophenyl ester (OPfp), a p-nitrophenyl ester (ONP) or an N-hydroxysuccinimide ester (OSu), and the combination of one of these methods with HOBT. If necessary, a base such as TEA, DIEA, NMM or 4-dimethylaminopyridine (DMAP) may be added to accelerate the reaction.

[0095]

When A or B is formyl, bond can be formed by conventional reductive bond forming reaction with amino group. When A or B is halomethylene or sulfonyloxymethylene, bond can be formed by substitution reaction with amino group.

[0096]

The compounds of the present invention can also be produced by applying the specific methods of production to

be described in the following Examples.

[0097]

[Examples]

On the pages that follow, the production of the compounds of the invention is described more specifically by reference to Examples, to which the invention is by no means limited.

[0098]

In order to demonstrate the utility of the compounds of the invention, typical examples of them were subjected to pharmacological tests on the motilin receptor antagonistic action and the results are described under Test Examples. The chemical structural formulae or chemical names of the compounds produced in Examples are set forth in Tables A-1 to A-8.

[0099]

[Table 1]

Table A-1

Example No.	Structural formula or chemical name
1	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
2	Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
3	Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
4	Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
5	Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2
6	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHSO_2Me$ TFAsalt
7	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe
8	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric 2- (3-tertbutyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide
9	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea
10	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine
11	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-cyano-N''-methylguanidine
12	2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tertbutyl-4-hydroxyphenyl)propylsulfamide

[0100]

[Table 2]

Table A-2

Example No.	Structural formula or chemical name
13	2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tertbutyl-4-hydroxyphenyl)propylaminoacetamide
14	N-[2-(3-tertbutyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2- [N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide
15	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide
16	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide
17	2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol
18	(2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone
19	2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone
20	5-(1-(2-((2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione
21	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

[0101]

[Table 3]

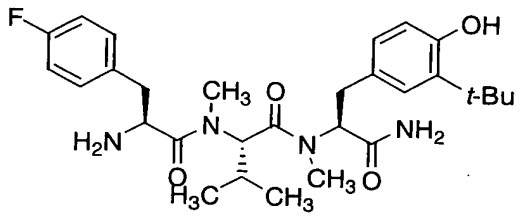
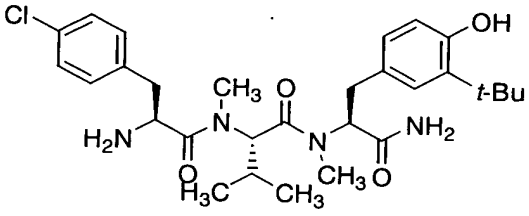
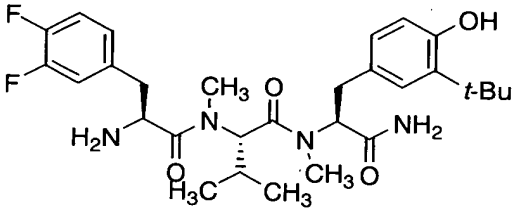
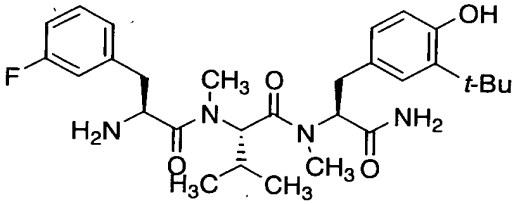
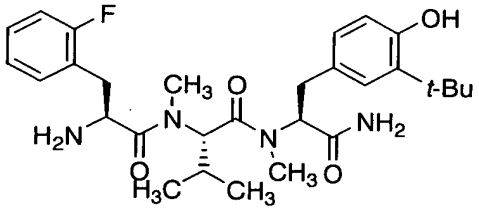
Table A-3

Example No.	Structural formula or chemical name
22	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide
23	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide
24	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide
25	2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

[0102]

[Table 4]

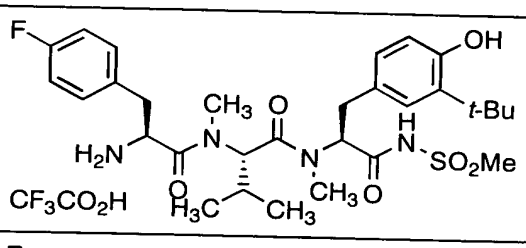
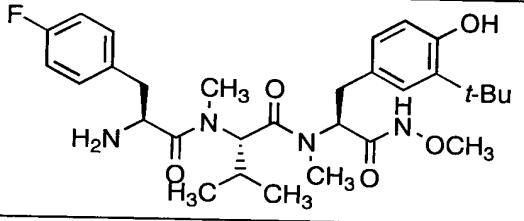
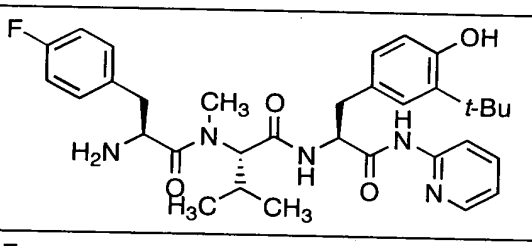
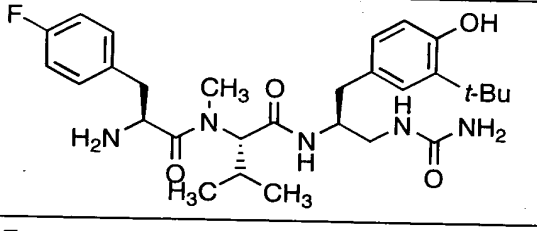
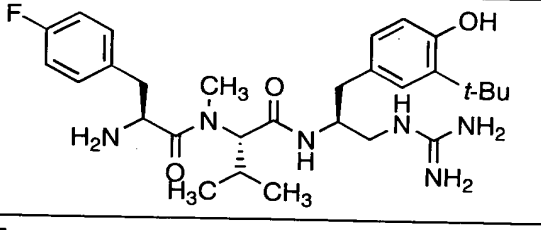
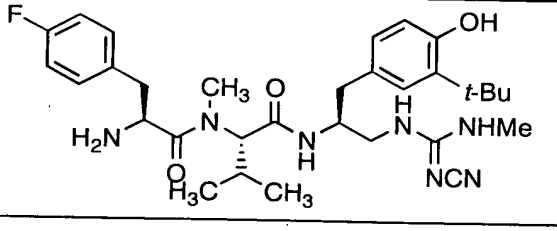
Table A-4

Example No.	Structural formula
1	
2	
3	
4	
5	

[0103]

[Table 5]

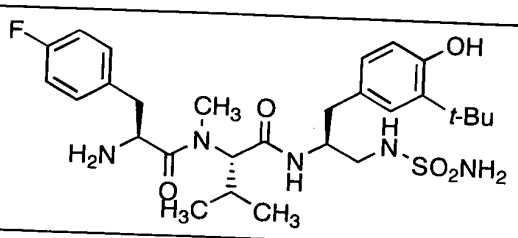
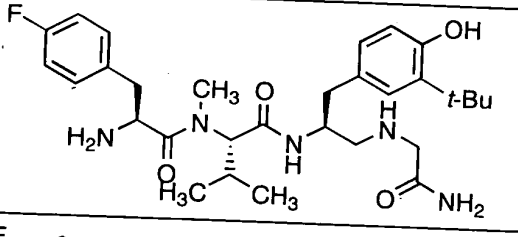
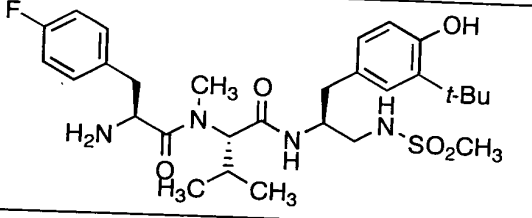
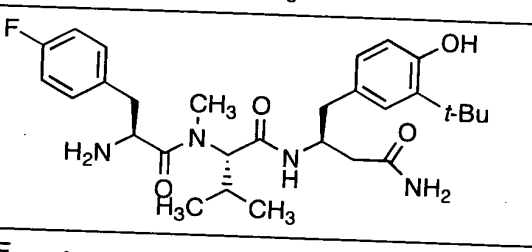
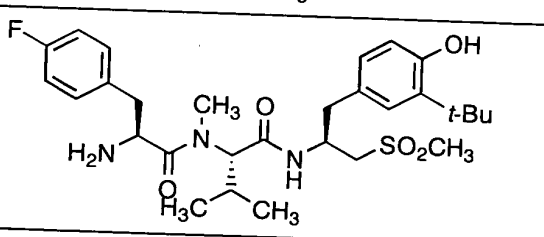
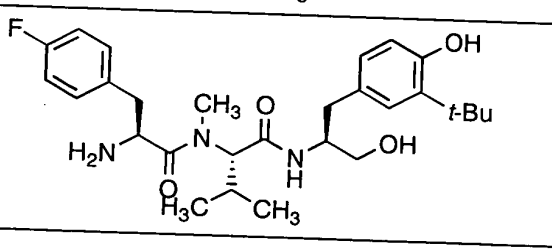
Table A-5

Example No.	Structural formula
6	
7	
8	
9	
10	
11	

[0104]

[Table 6]

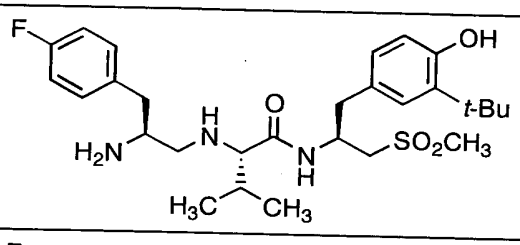
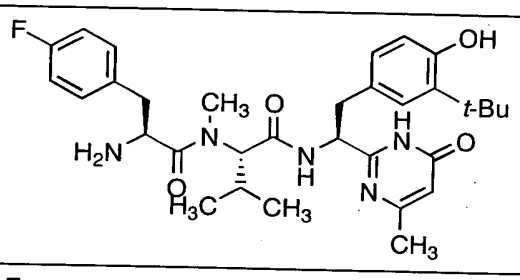
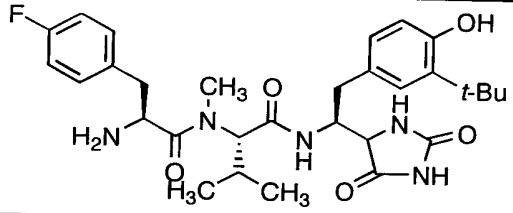
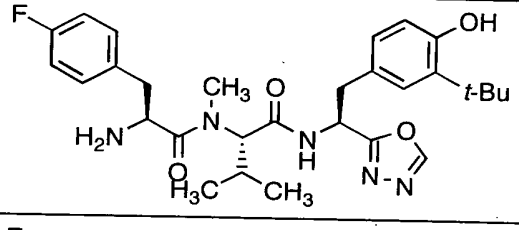
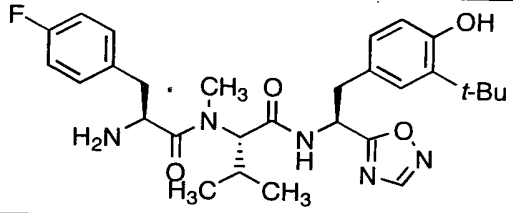
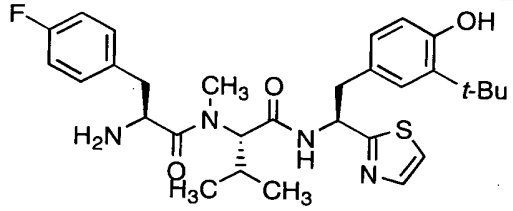
Table A-6

Example No.	Structural formula
12	
13	
14	
15	
16	
17	

[0105]

[Table 7]

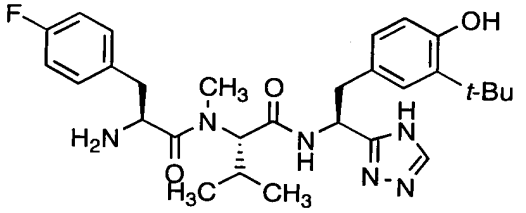
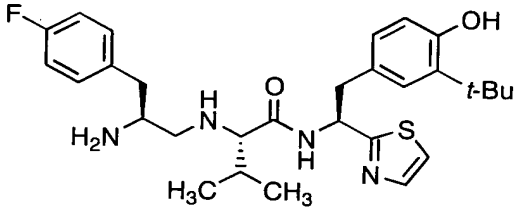
Table A-7

Example No.	Structural formula
18	
19	
20	
21	
22	
23	

[0106]

[Table 8]

Table A-8

Example No.	Structural formula
24	
25	

[0107]

In the following Examples, mass spectra (EI-MS) were taken by SHIMADZU GCMS-QP5050A or SHIMADZU GCMS-QP1000 and mass spectra (FAB-MS) were taken by JASCO 70-250SEQ.

[0108]

NMR was taken by JEOL JNM-EX-270 (270 MHz).

[0109]

Example 1

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Tyr(3-tBu)-OMe

To a solution of Tyr-OMe·HCl (500 g, 2.16 mol) in tert-butyl acetate (4500 ml), 70% $HClO_4$ (278 ml, 3.24 mol) was added and stirred for 4.5 days at room temperature. The reaction mixture was evaporated under reduced pressure; the thus obtained residue was dissolved in ethyl acetate,

poured into a saturated aqueous $NaHCO_3$ solution and stirred. The organic layer was collected and washed with a saturated aqueous $NaHCO_3$ solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with ether (950 ml) and at room temperature, stirred overnight. The thus precipitated crystals were collected by filtration to give Tyr(3-tBu)-OMe (242 g, 45%).

^{1}H-NMR($CDCl_3$): δ 1.38(9H,s), 2.83(1H,dd,J=13.7,7.4Hz), 3.02(1H,dd,J=13.7,5.1Hz), 3.70(1H,dd,J=7.4,5.1Hz), 3.73(3H,s), 6.55(1H,d,J=7.9Hz), 6.85(1H,dd,J=7.9,1.7Hz), 7.04(1H,d,J=1.7Hz)

(2) Synthesis of Z-Tyr(3-t-Bu)-OMe

To a solution of Tyr(3-tBu)-OMe (41.4 g, 0.165 mol) in 1,4-dioxane (170 ml) and H_2O (170 ml), under cooling with ice, sodium carbonate (26.2 g, 0.247 mol) was added and then Z-Cl (24.7 ml 0.173 mol) was further added over 25 min., followed by stirring for 2.5 hours at room temperature. The reaction mixture was mixed with water, extracted with chloroform, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus precipitated crystals were collected by filtration, washed with n-hexane and dried to give Z-Tyr(3-t-Bu)-OMe (54.7 g, 86%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 3.04(2H,brd,J=5.6Hz), 3.72(3H,s), 4.57-4.68(1H,m), 4.97(1H,brs), 5.10(2H,s), 5.20(1H,brd,J=7.9Hz), 6.55(1H,d,J=7.9Hz), 6.78(1H,dd,J=7.9,2.0Hz), 6.95(1H,d,J=2.0Hz), 7.26-

7.41(5H,m)

(3) Synthesis of Z-Phe(3-tBu-4-benzyloxy)-OMe

A solution of Z-Tyr(3-tBu)-OMe (1.0 g, 2.60 mmol), benzyl bromide (0.56 ml, 4.68 mmol) and potassium carbonate (1.08 g, 7.79 mmol) in DMSO (5 ml) was stirred overnight. The resulting mixture was mixed with a saturated aqueous ammonium chloride solution, extracted with ethyl acetate. The organic layer was washed with water and then saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5) to give Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g, 99%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 3.05(2H,d,J=5.6Hz), 3.71(3H,s), 4.60-4.68(1H,m), 5.06(2H,s), 5.09(2H,s), 5.24(1H,brd,J=8.3Hz), 6.82(1H,d,J=8.5Hz), 6.88(1H,dd,J=8.5,1.8Hz), 7.00(1H,d,J=1.8Hz), 7.27-7.50(10H,m)

(4) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2

To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g, 2.60 mmol) in 1,4-dioxane (30 ml), a 2N aqueous sodium hydroxide solution (3 ml) was added and stirred for 2 hours. The resulting mixture was mixed with water and washed with ethyl acetate; the aqueous layer was rendered acidic by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent

under reduced pressure, giving crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g).

To a solution of the thus obtained crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g) in THF (7 ml), under cooling with ice, methyl iodide (1.3 ml, 20.8 mmol) was added and then sodium hydride (60% in oil, 312 mg, 7.8 mmol) was added slowly, followed by stirring for 21 hours at room temperature. The resulting mixture was mixed with water, rendered acidic by the addition of dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g).

To a solution of the thus obtained crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g) in THF (25 ml), under cooling with ice, ethyl chloroformate (0.27 ml, 2.86 mmol) and NMM (0.31 ml, 2.86 mmol) were added in that order. The mixture was stirred for 15 min. and further stirred for another 15 min. while bubbling gaseous ammonia therein. The resultant mixture was left standing at room temperature, diluted with ethyl acetate and washed with water and then saturated brine. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1) to give Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2 (1.08 g, 88%, in 3 steps).

^{1}H-NMR($CDCl_3$): δ 1.37(9H,s), 2.87(3H,s), 2.86-2.99(1H,m), 3.21-3.35(1H,m), 4.73-4.95(1H,m), 5.06(2H,s), 5.09(2H,s), 5.67,5.83 and 6.13(3/2H,brs), 6.78-7.47(27/2H,m)

(5) Synthesis of N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH_2 (1.08 g, 2.28 mmol) in methanol (20 ml), 10% palladium/carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 96%).

^{1}H-NMR($CDCl_3$): δ 1.40(9H,s), 2.31(3H,s), 2.63(1H,dd,J=14.7,10.7Hz), 3.10-3.19(2H,m), 5.24(1H,brs), 5.38(1H,brs), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=7.9,1.8Hz), 7.05(1H,brs), 7.10(1H,d,J=1.8Hz)

(6) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-N-Me-Val-OH (700 mg, 2.64 mmol), N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 2.20 mmol) and CMPI (674 mg 2.64 mmol) in THF (22 ml), under cooling with ice, TEA (0.61 ml) was added and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-

hexane = 3:2) to give Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.98 g, 90%).

^{1}H-NMR($CDCl_3$):(four rotamers) δ 0.07, 0.32, 0.63, 0.74, 0.79, 0.81, 0.84 and 0.89(6H,d,J=6.3-6.6Hz), 1.30, 1.33, 1.37 and 1.39(9H,s), 2.13-2.33(1H,m), 2.34, 2.41, 2.78, 2.87 and 2.98(6H,s), 2.79-3.22(2H,m), 4.40 and 4.32(1H,d,J=10.6Hz), 4.60-5.43(5H,m), 5.96(1H,brs), 6.23-7.12(3H,m), 7.26-7.47(5H,m)

(7) Synthesis of N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (Intermediate I-b3 in the following Tables)

A mixture of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.98 g, 1.97 mmol) and 20% palladium hydroxide/carbon (0.10 g) in methanol (20 ml) was stirred at room temperature in a hydrogen atmosphere for 1.5 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.71 g, 99%).

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.35,0.71,0.92 and 0.96(6H,d,J=6.9Hz), 1.36 and 1.37(9H,s), 1.73-1.81 and 2.03-2.17(1H,m), 1.74 and 2.23(3H,s), 2.64(1H,d,J=9.2Hz), 2.90-3.04(1H,m), 2.93 and 3.00(3H,s), 3.19 and 4.60(1H,dd,J=14.7,5.8 and 10.7,3.8Hz), 5.29,5.32 and 6.06(2H,brs), 5.59(1H,dd,J=10.4,5.8Hz), 6.54 and 6.60(1H,d,J=7.9Hz), 6.79 and 6.93(1H,dd,J=7.9,2.0 and 1.7Hz), 7.01 and 7.07(1H,d,J=2.0 and 1.7Hz), 8.10(1H,brs)

(8) Synthesis of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Z-Phe(4-F)-OH (1.09 g, 3.44 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.04 g, 2.87 mmol) and CMPI (878 mg, 3.44 mmol) in THF (30 ml), TEA (0.96 ml, 6.88 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate =1:3) to give Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.73 g, 91%).

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.57,0.73,0.75 and 0.90(6H,d,J=6.3-6.6Hz), 1.33 and 1.39(9H,s), 2.18-3.43(5H,m), 2.40 and 3.03(3H,s), 2.74 and 3.01(3H,s), 4.62-5.49(7H,m), 5.95(1H,brs), 6.44(1H,d,J=7.9Hz), 6.57-7.35(12H,m)

(9) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

A mixture of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.73 g, 2.61 mmol) and 10% palladium/carbon (340 mg) in methanol (50 ml) was stirred at room temperature in a hydrogen atmosphere for 17 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (1.25 g, 91%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.50,0.76,0.79 and 0.93(6H,d,J=6.3-6.9Hz), 1.34 and 1.39(9H,s), 2.19-2.95(5H,m), 2.50 and 3.03(3H,s), 2.81 and 3.02(3H,s), 3.17 and 3.34(1H,dd,J=15.2,5.9 and 13.9,6.9Hz), 3.66 and 3.84(1H,dd,J=8.9,4.6 and 8.6,4.6Hz), 4.91 and 5.07(1H,d,J=10.6Hz), 5.07,5.19,5.30,5.98 and 6.64(2H,brs), 5.49(1H,dd,J=10.6,5.9Hz), 6.35 and 6.62(1H,d,J=7.9Hz), 6.74(2/3H,dd,J=7.9,1.7Hz), 6.95-7.11(19/3H,m)

[0110]

Example 2

Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(4-Cl)-OH (354 mg, 1.18 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.908 mmol) and CMPI (301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.05) to give Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.45 g, 77%).

(2) Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.45 g, 0.697 mmol) in methylene chloride (4 ml),

TFA (3 ml) was added, stirred for 20 min. and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with a saturated aqueous $NaHCO_3$ solution, and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 30:1:0.1) to give Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (355 mg, 93%).

EI-MS:544 and 546(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.49,0.75,0.78 and 0.93(6H,d,J=6.3-6.9Hz), 1.34 and 1.38(9H,s), 2.10-2.92(5H,m), 2.50 and 3.04(3H,s), 2.80 and 3.01(3H,s), 3.13 and 3.33(1H,dd,J=15.2,5.9 and 13.9,6.9Hz), 3.67 and 3.85(1H,dd,J=8.9,5.0 and 8.6,5.0Hz), 4.90 and 5.06(1H,d,J=10.6Hz), 5.33,5.41, 5.99 and 6.61(2H,brs), 5.49(1H,dd,J=10.6,5.9Hz), 6.37 and 6.63(1H,d,J=7.9Hz), 6.72 and 6.98(1H,dd,J=7.9,1.7Hz), 7.07-7.10(3H,m), 7.25-7.31(2H,m)

[0111]

Example 3

Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Fmoc-Phe(3,4-F_2)-OH (500 mg, 1.18 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.908 mmol) and CMPI (301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72

mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05), giving Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.56 g, 80%).

(2) Synthesis of Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Fmoc-Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.55 g, 0.715 mmol) in methylene chloride (5 ml), diethylamine (5 ml) was added, stirred for 4 hours and then evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:ethanol:aqueous ammonia = 60:1:0.1) to give Phe(3,4-F_2)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (381 mg, 97%).

EI-MS:546(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.51,0.74,0.79 and 0.93(6H,d,J=6.3-6.9Hz), 1.33 and 1.38(9H,s), 2.10-2.93(5H,m), 2.51 and 3.03(3H,s), 2.83 and 3.01(3H,s), 3.17 and 3.33(1H,dd,J=14.8,5.9 and 13.9,6.6Hz), 3.66 and 3.84(1H,dd,J=8.4,5.0 and 8.6,4.3Hz), 4.88 and 5.07(1H,d,J=10.6Hz), 5.41, 5.9(1H,brs), 5.41-5.51(1H,m), 6.43 and 6.64(1H,d,J=7.9Hz), 6.75(2/5H,dd,J=7.9,1.7Hz), 6.84-7.16(28/5H,m)

[0112]

Example 4

Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(3-F)-OH (0.20 g, 0.706 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.21 g, 0.578 mmol) and CMPI (0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05) to give Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 91%).

(2) Synthesis of Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.525 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added, stirred for 15 min. and then evaporated to remove the solvent under reduced pressure. The residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to

give Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (241 mg, 87%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.51,0.73,0.78 and 0.93(6H,d,J=6.3-6.6Hz), 1.33 and 1.38(9H,s), 2.10-2.96(5H,m), 2.46 and 3.03(3H,s), 2.78 and 3.01(3H,s), 3.16 and 3.35(1H,dd,J=14.8,5.9 and 13.9,6.6Hz), 3.70 and 3.90(1H,dd,J=8.3,5.6 and 8.6,5.0Hz), 4.89 and 5.06(1H,d,J=10.6Hz), 5.42, 5.99(1H,brs), 5.43-5.52(1H,m), 6.41 and 6.64(1H,d,J=7.9Hz), 6.72(2/5H,dd,J=7.9,1.7Hz), 6.83-6.99(18/5H,m), 7.10(2/5H,d,J=1.7Hz), 7.22-7.33(1H,m)

[0113]

Example 5

Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

(1) Synthesis of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(2-F)-OH (0.20 g, 0.706 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.21 g, 0.578 mmol) and CMPI (0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05) to give Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 91%).

(2) Synthesis of Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (0.33 g, 0.525 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added, stirred for 15 min. and then evaporated to remove the solvent under reduced pressure. The residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to give Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH_2 (235 mg, 85%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers) δ 0.45,0.71,0.79 and 0.93(6H,d,J=5.9-6.6Hz), 1.31 and 1.38(9H,s), 2.10-2.89(5H,m), 2.47 and 3.06(3H,s), 2.76 and 3.01(3H,s), 3.14 and 3.34(1H,dd,J=14.3,5.9 and 13.9,6.6Hz), 3.79 and 3.95(1H,dd,J=8.4,5.0 and 8.6,4.3Hz), 4.88 and 5.06(1H,d,J=10.6Hz), 5.37, 5.99(1H,brs), 5.41-5.51(1H,m), 6.43(3/5H,d,J=7.9Hz), 6.56(2/5H,brs), 6.60-6.71(1H,m), 6.92-7.29(6H,m)

[0114]

Example 6

TFA salt of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-$NHSO_2Me$

(1) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-$NHSO_2Me$

To a solution of crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (0.95 g, 2.0 mmol), WSCI·HCl (0.77 g, 3.99 mmol) and methanesulfonamide (0.29 g, 3.0 mmol) in DMF (15 ml), DMAP (0.49 g, 0.99 mmol) was added under cooling with ice and

stirred at room temperature overnight. The mixture was mixed with water and then with 2N hydrochloric acid, extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1) to give the titled compound (0.83 g, 75%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 2.80(s,3H), 2.97-3.30(m,2H), 3.21(s,3H), 4.60-4.74(m,1H), 5.08(s,2H), 5.13(s,2H), 6.81(d,1H,J=8.2Hz), 6.86-7.13(m,2H), 7.20-7.46(m,10H), 9.0(brs,1H)

(2) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$

A mixture of Z-N-Me-Tyr(3-tBu-4-benzyloxy)-$NHSO_2Me$ (0.80 g, 1.45 mmol) and 20% palladium hydroxide/carbon (0.09 g) in methanol (15 ml) was stirred at room temperature overnight in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (0.53 g).

To a solution of the crude N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (0.51 g, 1.43 mmol), Z-N-Me-Val-OH 0.49 g, 1.86 mmol) and CMPI (0.51 g, 2.00 mmol) in THF (10 ml), TEA (0.60 ml, 4.29 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water, rendered acidic by the addition of 2N hydrochloric acid and extracted with ethyl acetate. The organic layer

was washed with saturated brine, dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:3 containing 0.5% acetic acid) to give the titled compound (0.70 g, in 2 steps, 85%).

(3) Synthesis of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$

A mixture of Z-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (0.65 g, 1.13 mmol) and 20% palladium hydroxide/carbon (0.09 g) in methanol (10 ml) was stirred at room temperature for 2.5 hours in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (0.50 g).

To a solution of the above crude compound (0.48 g, 1.09 mmol), Boc-Phe(4-F)-OH 0.40 g, 1.41 mmol) and CMPI (0.39 g, 1.53 mmol) in THF (8 ml), TEA (0.46 ml, 3.27 mmol) was added under cooling with ice and stirred at room temperature overnight for 22 hours. The reaction mixture was mixed with water, rendered acidic by the addition of 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:3 containing 5% acetic acid) to give the titled compound

(0.50 g, in 2 steps, 65%).

(4) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ TFA salt

To a solution of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-$NHSO_2Me$ (208 mg, 0.294 mmol) in methylene chloride (6 ml), TFA (3 ml) was added and stirred for 1.5 hours. The reaction mixture was evaporated under reduced pressure; the thus obtained residue was dissolved in a mixture of acetonitrile/water (1:10) (80 ml), which mixture containing 0.1% TFA, and lyophilized to give the titled compound (0.20 g, 94%).

EI-MS:606(M^+)

^{1}H-NMR(DMSO-d_6):(three rotamers) δ 0.02(d,3/5H,J=5.9Hz), 0.22(d,3/5H,J=5.9Hz), 0.62(d,3/5H,J=7.6Hz), 0.68(d,3/5H,J=6.6Hz), 0.77(d,9/5H,J=6.6Hz), 0.89(d,9/5H,J=6.3Hz), 1.28(s,27/5H), 1.31(s,9/5H), 1.35(s,9/6H), 1.86-2.03(m,2/7H), 2.15-2.28(m,5/7H), 2.5-3.4(m,10H), 4.35-4.62(m,1H), 4.80-5.02(1H), 5.11-5.42(m,1H), 6.55-7.18(m,7H), 8.0-8.2(m,3H), 8.98-9.06(m,1H), 11.2(brs,1H)

[0115]

Example 7

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

(1) Synthesis of Z-N-Me-Phe(4-benzyloxy-3-tBu)-NHOMe

To a solution of Z-N-Me-Phe(4-benzyloxy-3-tBu)-OH (3.8 g, 7.99 mmol) in THF (50 ml), ethyl chloroformate (0.85 ml, 8.78 mmol) was added under cooling with ice and then NMM (0.97 ml, 8.78 mmol) was slowly added dropwise.

After stirring for 1 hour, $MeONH_2$ (1.0 g, 12.0 mmol) and TEA 2.23 ml (16.0 mmol) were added to the mixture, followed by stirring for 2 hours at room temperature. The mixture was mixed with water, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2) to give the titled compound (2.7 g, 67%).

^{1}H-NMR($CDCl_3$): δ 1.39(9H,s), 2.95(3H,s), 2.99(1H,m), 3.24(1H,m), 3.64(3H,s), 4.7(1H,m), 5.1(4H,d), 6.8-7.5(13H,m), 9.06(1H,s)

(2) Synthesis of N-Me-Tyr(3-tBu)-NHOMe

To a solution of Z-N-Me-Phe(4-benzyloxy-3-tBu)-NHOMe (2.7 g, 5.36 mmol) in MeOH (30 ml), palladium hydroxide /carbon (675 mg) was added and stirred in a hydrogen atmosphere for 2 hours. Insoluble matters were removed by filtration with Celite and the filtrate was concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1) to give the titled compound (1.24 g, 82%).

^{1}H-NMR($CDCl_3$): δ 1.43(9H,s), 2.45(3H,s), 2.92(2H,m), 3.12(1H,m), 3.59(3H,s), 6.77(1H,d,J=9.4Hz), 6.95(1H,dd,J=2.8,3.4Hz), 7.13(1H,d,J=3.15Hz)

(3) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of N-Me-Tyr(3-tBu)-NHOMe (1.24 g, 4.42 mmol), Z-N-Me-Val-OH (1.76 g, 6.63 mmol) and CMPI (1.7 g,

6.63 mmol) in THF (30 ml), TEA (1.23 ml, 8.84 mmol) was added and stirred overnight. The mixture was mixed with water, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1) to give the titled compound (1.32 g, 57%).

^{1}H-NMR($CDCl_3$): δ 0.43(3H,m), 0.80(3H,m), 1.36(9H,s), 3.02(9H,m), 3.65(3H,s), 4.4(1H,m), 5.1(3H,m), 6.4-7.4(8H,m)

(4) Synthesis of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (1.23 g, 2.33 mmol) in MeOH (20 ml), palladium hydroxide/carbon (350 mg) was added and stirred in a hydrogen atmosphere for 1 hour. Insoluble matters were removed by filtration with Celite and the filtrate was concentrated under reduced pressure to give crude N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (0.91 g).

A solution of the thus obtained crude compound (0.98 g, 2.5 mmol), Boc-Phe(4-F)-OH (0.92 g, 3.25 mmol) and CMPI (0.83 g, 3.25 mmol) in THF 20 ml, TEA (0.52 ml, 3.75 mmol) was added and stirred overnight. The mixture was mixed with water, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane

= 1:2), giving the titled compound (972 mg, 56%).

(6) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (972 mg, 1.508 mmol) in methylene chloride (10 ml), TFA (7 ml) was added and stirred for 30 min. The mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1), giving the titled compound (288 mg, 34%).

EI-MS:558(M^+)

^{1}H-NMR($CDCl_3$): δ 0.42(3H,d,J=13.5Hz), 0.79(3H,d,J=13.2Hz), 1.33(9H,s), 2.10(1H,m), 2.60(1H,m), 2.90(2H,m), 2.91(3H,s), 3.07(3H,s), 3.28(1H,m), 3.68(3H,s), 3.91(1H,m), 4.82(1H,d,J=10.7Hz), 5.13(1H,m), 6.60(1H,d,J=10.4Hz), 6.89(1H,m), 7.0-7.3(5H,m), 9.1(1H,m)

[0116]

Example 8

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

(1) Synthesis of N-benzyloxycarbonyl-3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide

To a solution of Z-Tyr(3-tBu)-OH (3.04 g, 8.19 mmol) in THF (8.2 ml), under cooling with ice N,N-carbonyldiimidazole (1.59 g, 9.83 mmol) was added and stirred for 1 hour. To the mixture, 2-aminopyridine (925 mg, 9.83 mmol) was then added and stirred for 2 hours under

cooling with ice and then further 6.5 hours at room temperature. The mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (2.16 g, 59%).

^{1}H-NMR($CDCl_3$): δ 1.24(9H,s), 2.95-3.20(2H,m), 4.45-4.60(1H,m), 5.11(2H,dd,J=17.5,12.2Hz), 6.53(1H,d,J=7.9Hz), 6.85(1H,d,J=7.9Hz), 6.95-7.15(2H,m), 7.32(5H,brs), 7.67-7.73(1H,m), 8.15-8.25(2H,m)

(2) Synthesis of 3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide

To a solution of N-benzyloxycarbonyl-3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide (2.16 g, 4.83 mmol) in methanol (160 ml), 10% palladium/carbon (400 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. After filtering the reaction mixture, the filtrate was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 10:1:100), giving the titled compound (1.48 g, 98%).

^{1}H-NMR($CDCl_3$): δ 1.36(9H,s), 2.72-3.23(2H,m), 3.67-3.72(1H,m), 6.62(1H,d,J=7.9Hz), 6.85-6.88(1H,m), 6.95-7.20(2H,m), 7.70-7.77(1H,m), 8.29-8.39(2H,m)

(3) Synthesis of 2-(N-benzyloxycarbonyl-N-methylamino)-3-

methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide (1.48 g, 4.73 mmol), Z-N-Me-Val-OH (1.63 g, 6.15 mmol) and CMPI (1.57 g, 6.15 mmol) in THF 30 ml, TEA (1.5 ml, 10.88 mmol) was added under cooling with ice and stirred for 3 hours under cooling with ice. The mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (1.74 g, 65%).

^{1}H-NMR($CDCl_3$): δ 0.70-0.95(6H,m), 1.26(9H,s), 2.20-2.35(1H,m), 2.70-3.10(5H,m), 4.00-4.20(1H,m), 4.65-4.80(1H,m), 5.17(2H,brs), 6.44(1H,d,J=7.6Hz), 6.60-6.85(1H,m), 6.95-7.10(2H,m), 7.36(5H,brs), 7.60-7.75(1H,m), 8.10-8.25(2H,m)

(4) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 2-(N-benzyloxycarbonyl-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.74 g, 3.10 mmol) in methanol (50 ml), 10% palladium carbon (300 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered

and the filtrate was concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 5:0.1:100), giving the titled compound (1.30 g, 98%).

^{1}H-NMR($CDCl_3$): δ 0.69(3H,d,J=6.9Hz), 0.85(3H,d,J=6.9Hz), 1.31(9H,s), 1.95-2.11(1H,m), 2.36(3H,s), 2.81(1H,d,J=4.6Hz), 2.99-3.18(2H,m), 4.73-4.81(1H,m), 6.59(1H,d,J=7.9Hz), 6.94(1H,dd,J=7.9,2.0Hz), 7.00-7.10(2H,m), 7.65-7.72(1H,m), 7.80(1H,d,J=7.9Hz), 8.18(1H,d,J=8.6Hz), 8.25(1H,d,J=4.6Hz),

(5) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.25 g, 2.93 mmol), Boc-Phe(4-F)-OH (1.08 g, 3.81 mmol) and CMPI (973 mg, 3.81 mmol) in THF 19 ml, TEA (0.94 ml, 6.74 mmol) was added under cooling with ice and stirred for 4 hours under cooling with ice. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.72 g, 85%).

^{1}H-NMR($CDCl_3$): δ 0.65-1.02(6H,m), 1.26(9H,s), 1.34(9H,s),

2.20-2.40(1H,m), 2.75-3.15(4H,m), 2.89(3H,s), 4.20-4.35(1H,m), 4.70-5.00(2H,m), 6.61(1H,d,J=7.9Hz), 6.75-7.20(7H,m), 7.60-7.80(1H,m), 8.20-8.30(2H,m)

(6) 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.67 g, 2.41 mmol) in methylene chloride (30 ml), TFA (5 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated under reduced pressure; the thus obtained residue was mixed with chloroform, washed with a saturated aqueous $NaHCO_3$ solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (370 mg).

EI-MS:591(M^+)

^{1}H-NMR($CDCl_3$): δ 0.74(2H,d,J=6.9Hz), 0.77(1H,d,J=6.9Hz), 0.88(1H,d,J=6.3Hz), 0.95(2H,d,J=6.3Hz), 1.25(9H,s), 2.24-2.44(1H,m), 2.50-3.25(4H,m), 2.78(2.4H,s), 2.85(0.6H,s), 3.55-3.65(0.8H,m), 3.80-3.90(0.2H,m), 4.00(0.8H,d,J=10.9Hz), 4.36(0.2H,d,J=10.9Hz), 4.65-4.80(0.2H,m), 4.90-5.00(0.8H,m), 6.55-7.20(8H,m), 7.65-7.75(1H,m), 8.15-8.25(2H,m)

[0117]

Example 9

N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

(1) Synthesis of Z-3-tBu-tyrosinol

To a solution of Z-Tyr(3-tBu)-OMe (7.4 g, 19 mmol) in THF (190 ml), lithium borohydride (1.25 g, 57.4 mmol) was added under cooling with ice and stirred for 1.5 hours at room temperature. The mixture was mixed with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (6.8 g, 99%).

^{1}H-NMR($CDCl_3$): δ 1.38(9H,s), 2.15(1H,m), 2.78(2H,brd,J=6.9Hz), 3.5-3.8(2H,m), 3.8-4.0(1H,m), 4.86(1H,s), 4.9-5.0(1H,m), 5.09(2H,s), 6.58(1H,d,J=7.9Hz), 6.88(1H,brd,J=7.9Hz), 7.05(1H,brs), 7.34(5H,s)

(2) Synthesis of 2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine

To a solution of Z-3-tBu-tyrosinol (2 g, 5.6 mmol), triphenylphosphine (1.76 g, 6.7 mmol), phthalimide (0.99 g, 6.7 mmol) in THF 50 ml, diethyl azodicarboxylate (DEAD) (1.05 ml, 6.7 mmol) was added under cooling with ice and stirred at the same temperature for 1 hour. The mixture was mixed with water and extracted with ethyl acetate. The

organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1) to give (1-(1,3-dihydro-1,3-dioxo-isoindol-2-yl)methyl-2-(3-tBu-4-hydroxyphenyl)ethyl)carbamic acid benzyl ester (3.2 g).

To the above compound (3.2 g), a 40% methylamine methanol solution (40 ml) was added at room temperature and stirred at the same temperature for 10 hours. The reaction mixture was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (1.9 g).

^{1}H-NMR($CDCl_3$): δ 1.37(9H,s), 2.6-2.9(4H,m), 3.7-3.9(4/5H,m), 3.9-4.1(1/5H,m)4.8-4.9(4/5H,m), 5.09(2H,s), 5.4-5.5(1/5H,m), 6.5-6.6(1H,m), 6.84(1H,d,J=7.3Hz), 6.9-7.1(1H,m), 7.33(5H,s)

(3) Synthesis of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

A mixture of 2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (1.0 g, 2.8 mmol), potassium cyanate (0.5 g, 5.5 mmol), acetic acid (0.5 ml), dioxane (10 ml) and water (10 ml) was stirred at 60°C for 2 hours. The mixture was mixed with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous

magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:methanol = 50:1), giving the titled compound (0.9 g, 80%).

^{1}H-NMR(CD_3OD): δ 1.35(9H,s), 2.5-2.8(2H,m), 3.0-3.2(1H,m), 3.2-3.4(1H,m), 3.7-3.9(1H,m), 5.01(2H,d,J=3.6Hz), 6.63(1H,d,7.9Hz), 6.84(1H,brd,J=7.9Hz), 7.04(1H,brs), 7.2-7.4(5H,m)

(4) Synthesis of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.9 g, 2.26 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 12 hours. After filtration, the filtrate was concentrated under reduced pressure to give N-(2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.54 g).

To a solution of the above compound (0.53 g, 2 mmol), Z-N-Me-Val-OH (0.69 g, 2.6 mmol) and CMPI (0.67 g, 2.6 mmol) in THF (20 ml), TEA (1 ml, 7.2 mmol) was added under cooling with ice and stirred at room temperature for 1.5 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent:

chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (0.98 g, 98%).

^{1}H-NMR($CDCl_3$): δ 0.82(3H,d,J=6.3Hz), 0.88(3H,d,J=6.3Hz), 1.35(9H,s), 2.1-2.3(1H,m), 2.6-2.8(2H,m), 2.76(3H,s), 3.0-3.4(2H,m), 3.9-4.1(1H,m), 4.7-5.0(2H,m), 5.0-5.1(2H,m), 5.5-5.6(1H,m), 6.4-7.0(5H,m), 7.34(5H,s)

(5) Synthesis of N-(2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.97 g, 1.95 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 3 hours. After filtering the reaction mixture, the filtrate was evaporated to remove the solvent under reduced pressure, giving N-(2-(2-amino-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.72 g).

To a solution of the above crude compound (0.64 g, 1.85 mmol), Boc-Phe(4-F)-OH (0.63 g, 2.22 mmol) and CMPI (0.57 g, 2.23 mmol) in THF (18 ml), TEA (0.93 ml, 6.67 mmol) was added under cooling with ice and stirred at room temperature for 8 hours. The mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent:

chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (0.79 g, 66%).

^{1}H-NMR(DMSO-d_6): δ 0.70, 0.75, 0.85, and 0.95(6H,d,J=5.9-6.3Hz), 1.2-1.4(18H,m), 2.0-2.1(1H, m), 2.4-2.9(7H,m), 2.9-3.1(2H,m), 3.8-4.0(1H,m), 4.3-4.6(2H,m), 5.39, 5.51(2H,brs), 5.74(1H,d,J=1.3Hz), 5.9-6.0(1H,m), 6.6-6.9(2H,m), 6.9-7.1(2H,m), 7.1-7.3(3H,m), 7.60 and 7.73(1H, brd), 9.02(1H,s)

(6) Synthesis of N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.75 g) in methylene chloride (6 ml), TFA (6 ml) was added under cooling with ice, stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (480 mg, 76%).

FAB-MS:544(M^++1)

^{1}H-NMR(DMSO-d_6): δ 0.49, 0.73, and 0.85(6H,d,J=6.0-6.6Hz), 1.30 and 1.32(9H,s), 2.0-2.2(1H,m), 2.4-3.1(9H,m), 3.7-

4.1(3H,m), 4.52 and 5.48(total 2H,m), 5.8-6.0(1H,m), 6.6-6.8(2H,m), 6.9-7.3(5H,m), 7.67 and 8.79(1H,d,J=7.6-8.6Hz), 9.01 and 9.06(1H,s)

[0118]

Example 10

N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine

(1) Synthesis of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of (2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)amine (1.46 g, 4.1 mmol) in dioxane (8 ml), an aqueous sodium carbonate solution (0.44 g, 4.1 mmol) (8 ml) and $(Boc)_2O$ (0.9 g, 4.1 mmol) were added in that order under cooling with ice and stirred at the same temperature for 2.5 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (1.7 g, 91%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 1.42(9H,s), 2.6-2.9(2H,m), 3.1-3.3(2H,m), 3.8-4.0(1H,m), 4.7-4.8(1H,m), 5.08(2H,s), 6.58(1H,d,J=8.9Hz), 6.85(1H,brd,J=8.9Hz), 7.03(1H,brs), 7.2-7.5(5H,m)

(2) Synthesis of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-

3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.6 g, 3.5 mmol) in methanol (35 ml), 10% palladium carbon (160 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1.5 hours. After filtration, the filtrate was concentrated under reduced pressure to give N-((2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.1 g).

To a solution of the thus obtained crude compound (1.1 g, 3.42 mmol), Z-N-Me-Val-OH (1.08 g, 4.08 mmol) and CMPI (1.04 g, 4.07 mmol) in THF (35 ml), TEA (1.7 ml, 12.2 mmol) was added under cooling with ice and stirred at room temperature for 1 hour. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (1.8 g, 93%).

^{1}H-NMR($CDCl_3$):δ 0.82(3H,d,J=6.6Hz), 0.90(3H,d,J=6.2Hz), 1.37(9H,s), 1.42(9H,s), 2.1-2.3(1H,m), 2.5-2.8(5H,m), 3.0-3.3(2H,m), 3.9-4.3(2H,m), 5.13(2H,s), 6.44(1H,d,J=7.9Hz), 6.75(1H,brd,J=7.9Hz), 7.00(1H,brs), 7.36(5H,s)

(3) Synthesis of N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-

hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.8 g, 3.16 mmol) in methanol (35 ml), 10% palladium carbon (180 mg) was added and stirred for 1 hour in a hydrogen atmosphere at room temperature. After filtration, the filtrate was concentrated under reduced pressure to give N-(2-(2-(N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.33 g).

To a solution of the thus obtained crude compound (1.33 g, 3.15 mmol), Z-Phe(4-F)-OH (1.2 g, 3.78 mmol) and CMPI (0.97 g, 3.78 mmol) in THF (35 ml), TEA (1.6 ml, 11.5 mmol) was added under cooling with ice and stirred at room temperature for 10 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.48 g, 53%).

^{1}H-NMR($CDCl_3$):δ 0.68, 0.75, 0.91, and 0.98(6H,d,J=6.2-6.9Hz), 1.35,1.37,1.40, and 1.42(18H,m), 2.1-3.4(10H,m), 4.0-4.5, 4.7-5.1, and 5.5-5.7(7H,m), 6.3-7.5(17H, m)

(4) Synthesis of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine

To a solution of N-(2-(2-((2-

(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.38 g) in methylene chloride (5 ml), TFA (5 ml) was added under cooling with ice, stirred at room temperature for 30 min. and evaporated under reduced pressure to remove the solvent. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (1.1 g, 92%).
^{1}H-NMR($CDCl_3$):δ 0.67,0.76,0.92,and 0.97(6H,d,J=6.6-6.9Hz), 1.35 and 1.37(9H,s), 2.2-2.5(1H,m), 2.4-3.1(9H,m), 4.0-4.2 and 4.4-4.5(2H,m), 4.7-5.1(2H,m), 5.5-5.6 and 5.7-5.9(1H,brd,J=7.6-8.1Hz), 6.2-6.4, 6.5-6.7, and 6.8-7.4(13H,m)

(5) Synthesis of N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine

To a solution of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (580 mg, 0.91 mmol) in DMF (4.5 ml), 1H-pyrazole-1-carboxamidine hydrochloride (161 mg, 1.09 mmol) and DIEA (0.19 ml, 1.09 mmol) were added at room temperature and

stirred at the same temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (aminopropylated silica gel (CHROMATOREX NH-DM1020, FUJI SILYSIA CHEMICAL LTD.), developing solvent: ethyl acetate:methanol = 100:1 to 10:1) to give N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine (410 mg).

To a solution of the above compound (410 mg) in methanol (20 ml), 10% palladium carbon (40 mg) was added and stirred in a hydrogen atmosphere at room temperature for 5 hours. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (aminopropylated silica gel (CHROMATOREX NH-DM1020, FUJI SILYSIA CHEMICAL LTD.), developing solvent: ethyl acetate:methanol =5:1), giving the titled compound (250 mg, 76%).

FAB-MS:543(M^++1)

^{1}H-NMR(CD_3OD)):δ 0.47, 0.53, 0.80, 0.90(6H,d,J=6.3-6.9Hz), 1.31, 1.37(9H,s), 2.0-2.3(1H,m), 2.41, 2.46, and 2.57(3H,s), 2.5-3.4(6H,m), 3.8-4.6(3H,m), 6.6-7.3(7H,m)

[0119]

Example 11

Synthesis of N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-

cyano-N''-methylguanidine

To a solution of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (500 mg, 0.79 mmol) in ethanol (4 ml), dimethyl N-cyanodithioiminocarbonate (127 mg, 0.87 mmol) was added at room temperature and stirred at the same temperature for 16 hours. The reaction mixture was concentrated under reduced pressure; the thus obtained residue was mixed with a 40% methylamine methanol solution (5 ml) at room temperature and stirred at the same temperature for 16 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1) to give N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-cyano-N''-methylguanidine (450 mg).

To a solution of the above compound (440 mg) in methanol (6 ml), 10% palladium carbon (50 mg) was added and stirred in a hydrogen atmosphere at room temperature for 15 hours. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (280 mg, 78%).

FAB-MS:582(M^++1)

^{1}H-NMR($CDCl_3$):δ 0.62, 0.79, 0.87, and 0.91(6H,d,J=6.3-6.6Hz), 1.37 and 1.40(9H,s), 2.1-2.4(1H,m), 2.5-3.0(10H,m), 3.1-3.4(2H,m), 3.6-4.4(3H,m), 5.8-6.1(1H,m), 6.6-7.2(7H,m), 8.68(1H,d,J=6.6Hz)

[0120]

Example 12

2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

(1) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylamine (514 mg, 0.811 mmol) in 1,4-dioxane (8 ml), sulfamide (156 mg, 1.62 mmol) was added and stirred at 120°C for 5 hours. The reaction mixture was evaporated under reduced pressure to remove the solvent; the thus obtained residue was mixed with water, and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1), giving the titled compound (397 mg, 69%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.69,0.85 and 0.99(6H,d,J=6.3-6.6Hz), 1.36 and 1.37(9H,s), 1.80-1.90(1H,m), 2.22-2.40(1H,m), 2.43 and 2.81(3H,s), 2.60-3.10(4H,m), 3.26-3.38(1H,m), 3.70-3.80(1H,m), 3.90-4.10(1H,m),4.28-4.44(1H,m), 4.72-5.30(3H,m), 5.03(2H,s), 6.52-6.66(2H,m), 6.80-7.40(10H,m)

(2) Synthesis of 2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

A mixture of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide (332 mg, 0.466 mmol) and 10% palladium carbon (40 mg) in methanol (5 ml) was stirred at room temperature in a hydrogen atmosphere overnight. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 200:10:1), giving the titled compound (180 mg, 67%).

FAB-MS:580($M+H^+$)

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.63,0.75,0.81 and 0.93(6H,d,J=6.3-6.6Hz), 1.38 and 1.39(9H,s), 2.20-3.42(6H,m), 2.60 and 3.02(3H,s), 3.49(1H,s), 3.60-3.90(2H,m), 4.30-4.44(1H,m), 5.30-5.40(1H,m), 6.56-7.16(7H,m), 8.34-8.42(1H,m)

[0121]

Example 13

2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

(1) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetic acid ethyl ester

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylamine (1.17 g, 1.84 mmol) in ethanol (18 ml), ethyl glyoxylate (0.7 ml, 2.76 mmol), acetic acid (1.8 ml) and sodium cyanoborohydride (173 mg, 2.76 mmol) were added and stirred for 1 hour. The reaction mixture was mixed with a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate and washed with saturated brine. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate:methylene chloride = 2:3:1), giving the titled compound (900 mg, 68%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.65,0.75,0.91 and 0.97(6H,d,J=6.2-6.9Hz), 1.22 and 1.29(3H,t,J=7.2Hz), 1.35 and 1.36(9H,s), 2.22-2.40(1H,m), 2.42 and 2.90(3H,s), 2.60-3.02(5H,m), 3.22-3.46(2H,m), 4.06-4.28(2H,m), 4.47(1H,d,J=12.2Hz), 4.80-5.12(3H,m), 5.29(2H,s), 5.74(1H,d,J=8.9Hz), 6.58-7.42(12H,m)

(2) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetic acid ethyl ester (889 mg, 1.23 mmol) in methanol (24 ml), aqueous ammonia (16 ml) was added and stirred for 15 hours at room temperature. The reaction mixture was evaporated to remove the solvent under reduced pressure, extracted with ethyl acetate and washed with saturated brine. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 110:10:1), giving the titled compound (600 mg, 70%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.65,0.75,0.90 and 0.96(6H,d,J=6.0-6.6Hz), 1.36 and 1.37(9H,s), 2.22-2.40(1H,m), 2.47 and 2.82(3H,s), 2.60-3.02(4H,m), 3.24 and 3.26(2H,s), 4.02-4.38(2H,m), 4.76-5.08(3H,m), 5.40-5.90(3H,m), 6.56-7.38(12H,m)

(3) Synthesis of 2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-

methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide (595 mg, 0.860 mmol) in methanol (10 ml), 20% palladium hydroxide/carbon (150 mg) was added and stirred at room temperature in a hydrogen atmosphere overnight. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol:hexane = 10:1:1), giving the titled compound (333 mg, 70%).

FAB-MS:558($M+H^+$)

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.66,0.79 and 0.92(6H,d,J=6.3-6.6Hz), 1.36 and 1.39(9H,s), 2.22-2.38(1H,m), 2.63 and 2.91(3H,s), 2.50-2.82(4H,m), 3.12-3.28(2H,m), 3.58-3.88(2H,m), 4.18-4.40(2H,m), 5.50-5.70(1H,m), 6.58-7.14(8H,m)

[0122]

Example 14

N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide

(1) Synthesis of N-Z-2-(4-benzyloxy-3-tert-butylphenyl)-1-hydroxymethylethylamine

To a solution of Z-Phe(4-benzyloxy-3-tBu)-OMe (5.8 g, 12.2 mmol) in methanol/water (100 ml/20 ml), sodium borohydride (1.5 g, 36.6 mmol) was added and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl

acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (5.1 g, 94%).

(2) Synthesis of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropylamine

To a solution of N-Z-2-(4-benzyloxy-3-tert-butylphenyl)-1-hydroxymethylethylamine (5.09 g, 11.4 mmol), triphenylphosphine (4.41 g, 17.1 mmol) and phthalimide (2.51 g, 17.1 mmol) in THF (66 ml), diethyl azodicarboxylate (3.0 ml, 17.1 mmol) was added and stirred for 4 hours under cooling with ice. The reaction mixture was concentrated; a solution of the thus obtained residue in methanol (70 ml) was mixed with hydrazine (6 ml) and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (2.45 g, 49%).

(3) N-[3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropyl]methanesulfonamide

To a solution of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropylamine (1.27 g, 2.84 mmol) in

methylene chloride (29 ml), TEA (0.6 ml, 4.26 mmol) and then methanesulfonyl chloride (0.3 ml, 3.69 mmol) were added slowly under cooling with ice. After stirring for 30 min., the mixture was mixed with water and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:1:2), giving the titled compound (1.23 g, 83%).

(4) Synthesis of 2-[N-(benzyloxycarbonyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide

N-[3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropyl]methanesulfonamide (1.2 g, 2.29 mmol) was dissolved in a mixture of methanol (23 ml) and methylene chloride (5 ml), mixed with palladium hydroxide/carbon (0.60g) and stirred for 12 hours in a hydrogen atmosphere. After filtering off insoluble material using Celite, the filtrate was concentrated to give crude N-[2-amino-3-(4-benzyloxy-3-tert-butylphenyl)propyl]methanesulfonamide (0.68 g).

^{1}H-NMR($CDCl_3$):δ 1.39(s,9H), 2.48(dd,1H,J=8.2,13.9Hz), 2.73(dd,1H,J=5.1,13.3Hz), 2.94(dd,1H,J=7.9,11.9Hz), 2.96(s,3H), 3.10-3.22(m,1H), 3.24(dd,1H,J=3.6,12.2Hz), 6.60(d,1H,J=7.9Hz), 6.83(dd,1H,J=2.0,7.9Hz), 7.03(d,1H,J=2.0Hz)

To a solution of the above crude compound (0.66 g),

Z-N-Me-Val-OH (758 mg, 2.86 mmol) and CMPI (730 mg, 2.86 mmol) in THF (22 ml), TEA (0.91 ml, 6.59 mmol) was added under cooling with ice. The resultant was stirred overnight at room temperature, mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:3:2), giving the titled compound (1.08 g, 90%).

(5) Synthesis of 2-[N-(N-benzyloxycarbonyl-4-fluorophenylalaninoyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide

To a solution of 2-[N-(benzyloxycarbonyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide (1.0 g, 1.83 mmol) in methanol (18 ml), palladium hydroxide/carbon (0.40 g) was added and stirred in a hydrogen atmosphere for 1.5 hours. After filtering off insoluble material using Celite, the filtrate was concentrated; to a solution of the thus obtained residue (0.75 g), Z-Phe(4-F)-OH (748 mg, 2.66 mmol) and CMPI (602 mg, 2.36 mmol) in THF 18 ml, TEA (0.82 ml, 5.44 mmol) was added under cooling with ice. The mixture was stirred at room temperature overnight, mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl

acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:3:2), giving the titled compound (827 mg, 64%).

(6) Synthesis of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide

To a solution of 2-[N-(N-benzyloxycarbonyl-4-fluorophenylalaninoyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide (680 mg, 0.95 mmol) in methanol (10 ml), palladium hydroxide/carbon (0.25 g) was added and stirred in a hydrogen atmosphere for 1 hour. After filtering off insoluble material using Celite, the filtrate was concentrated; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:concentrated aqueous ammonia = 100:10:1), giving the titled compound (494 mg, 89%).

EI-MS:578(M^+)

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.62(d,21/10H,J=6.9Hz), 0.75(d,9/10H,J=6.6Hz), 0.84(d,9/10H,J=6.6Hz), 0.93(d,21/10H,J=6.3Hz), 1.36(s,27/10H), 1.39(s,63/10H), 2.20-2.45(m,1H), 2.46-2.95(m,8H), 3.02-3.17(m,3H), 3.61-4.05(m,2H), 4.18-4.37(m,1H), 4.87-4.95(m,7/10H), 5.23-5.35(m,3/10H), 5.55-5.70(m,3/10H), 6.20-6.50(m,7/10H), 6.60-7.20(m,7H), 8.01(d,1H,J=7.6Hz)

[0123]

Example 15

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

(1) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethyl carbamic acid benzyl ester

To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (2.46 g, 5.19 mmol) in THF (50 ml), lithium borohydride (339 mg, 15.57 mmol) was added under cooling with ice and stirred at room temperature for 3 hours. The reaction mixture was mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (2.30 g, 99%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.11(1H,brs), 2.80(2H,d,J=6.9Hz), 3.54-3.77(2H,m), 3.83-3.97(1H,m), 4.88-4.97(1H,m), 5.09(4H,s), 6.85(1H,d,J=8.3Hz), 6.97(1H,dd,J=8.3,1.8Hz), 7.11(1H,d,J=1.8Hz), 7.27-7.50(10H,m)

(2) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonyloxymethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethylcarbamic acid benzyl ester (1.87 g, 4.18 mmol) in pyridine (42 ml), methanesulfonyl chloride (0.36

ml, 4.60 mmol) was added under cooling with ice. After stirring for 1 hour, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving the titled compound (1.93 g, 88%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.76-2.92(2H,m), 2.96(3H,s), 4.10-4.21(2H,m), 4.21-4.32(1H,m), 4.88-5.00(1H,m), 5.09(4H,s), 6.86(1H,d,J=8.6Hz), 6.98(1H,brd,J=7.9Hz), 7.11(1H,brs), 7.30-7.48(10H,m)

(3) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonyloxymethylethylcarbamic acid benzyl ester 1.93 g, 4.23 mmol) in DMSO (11 ml), potassium cyanide (827 mg, 12.7 mmol) was added and heated at 70°C. After stirring for 4 hours, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (1.42 g, 74%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.46(1H,dd,J=16.8,4.0Hz), 2.74(1H,dd,J=16.8,4.6Hz), 2.82(1H,dd,J=13.8,8.4Hz), 2.96(1H,dd,J=13.8,6.5Hz), 4.07-4.18(1H,m), 4.89-4.98(1H,m), 5.09(4H,s), 6.87(1H,d,J=8.3Hz), 6.99(1H,dd,J=8.3,1.5Hz), 7.12(1H,d,J=1.5Hz), 7.36-7.47(10H,m)

(4) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamine

To a solution of 2-(4-benzyloxy-3-tbutylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester (1.38 g, 3.03 mmol) in DMSO (24 ml), potassium carbonate (1.59 g) and 30% hydrogen peroxide (4.0 ml) were added under cooling with ice. After stirring at room temperature for 2 hours, the reaction mixture was mixed with water; the thus formed precipitates were collected by filtration to give 2-(4-benzyloxy-3-t-butylphenyl)-1-carbamidemethylethylcarbamic acid benzyl ester.

A mixture of the above crude compound, 20% palladium hydroxide/carbon (0.50 g) and methanol (30 ml) was stirred at room temperature in a hydrogen atmosphere for 8 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (639 mg, 84%).

^{1}H-NMR(DMSO):δ 1.33(9H,s), 1.96(1H,dd,J=14.5,8.6Hz), 2.12(1H,dd,J=14.5,4.0Hz), 2.37(1H,dd,J=13.4,7.4Hz), 2.46-2.55(1H,m), 3.07-3.20(1H,m), 6.68(1H,d,J=8.2Hz), 6.73(1H,brs), 6.79(1H,brd,J=8.2Hz), 7.40(1H,brs), 9.05(1H,s)

(5) Synthesis of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

To a solution of Z-N-Me-Val-OH (736 mg, 2.78 mmol),

2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamine (579 mg, 2.32 mmol) and CMPI (710 mg, 2.78 mmol) in THF (23 ml), TEA (0.77 ml) was added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving the titled compound (1.09 g, 95%).

^{1}H-NMR($CDCl_3$):δ 0.78-0.90(6H,m), 1.37(9H,s), 2.14-2.80(5H,m), 2.72(3H,s), 3.92-4.04(1H,m), 4.32-4.48(1H,m), 5.04,5.15(2H,brs), 5.27-5.37(1H,m), 5.78,6.03(1H,brs), 6.38-6.82(3H,m), 7.04(1H,brs), 7.30-7.41(5H,m).

(6) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

To a solution of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (1.04 g, 2.09 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 hour. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.67 g, 88%).

^{1}H-NMR($CDCl_3$):δ 0.68(3H,d,J=6.9Hz), 0.83(3H,d,J=6.9Hz),

1.38(9H,s), 1.82-1.97(1H,m), 2.27(3H,s), 2.45(1H,dd,J=15.8,7.3Hz), 2.68(1H,d,J=4.6Hz), 2.78-2.91(2H,m), 4.41-4.56(1H,m), 5.30(1H,brs), 5.58(1H,brs), 6.34(1H,brs), 6.62(1H,d,J=8.0Hz), 6.92(1H,dd,J=8.0,2.0Hz), 7.04(1H,d,J=2.0Hz), 7.63(1H,brd,J=8.9Hz)

(7) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

To a solution of Z-Phe(4-F)-OH (650 mg, 2.05 mmol), 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (0.62 g, 1.71 mmol) and CMPI (524 mg, 2.05 mmol) in THF (17 ml), TEA (0.57 ml, 4.10 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving 2-((2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (1.05 g, 93%).

A mixture of the above compound (1.16 g, 1.75 mmol) and 10% palladium carbon (120 mg) in methanol (18 ml) was stirred at room temperature in a hydrogen atmosphere for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained

residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (761 mg, 82%).

EI-MS:528(M^+)

^{1}H-NMR($CDCl_3$):δ 0.67,0.80,0.90,0.92(6H,d,J=6.3-6.9Hz), 1.37, 1.39(9H,s), 2.21-3.22(6H,m), 2.61,2.89(3H,s), 3.59-3.88,4.34-4.48(3H,m), 5.33,5.42(1H,brs), 5.90,6.07(1H,brs), 6.56-7.18(7H,m), 8.71(1H,brd,J=8.3Hz)

[0124]

Example 16

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

(1) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-toluenesulfonyloxymethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethylcarbamic acid benzyl ester (2.07 g, 4.63 mmol) in pyridine (46 ml), toluenesulfonyl chloride (6.79 g, 35.6 mmol) was added under cooling with ice. After stirring for 6.5 hours, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (2.46 g, 88%).

^{1}H-NMR($CDCl_3$):δ 1.36(9H,s), 2.42(3H,s), 2.72-2.86(2H,m),

3.92-4.09(3H,m), 4.84-4.95(1H,m), 5.04(2H,s), 5.07(2H,s), 6.79(1H,d,J=8.0Hz), 6.87(1H,brd,J=8.0Hz), 7.06(1H,brs), 7.26-7.48(12H,m), 7.76(2H,d,J=8.3Hz)

(2) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methylthiomethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-toluenesulfonyloxymethylethylcarbamic acid benzyl ester 2.4 g, 3.99 mmol) in ethanol (40 ml), a solution of sodium methanethiolate (560 mg, 7.99 mmol) in methanol (4 ml) was added and stirred at 40°C for 3 hours. The mixture was evaporated under reduced pressure to remove the solvent, mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 5:1), giving the titled compound (1.63 g, 86%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.12(3H,s), 2.61(2H,d,J=5.6Hz), 2.85(2H,d,J=6.3Hz), 3.99-4.12(1H,m), 4.80-4.91(1H,m), 5.09(4H,s), 6.85(1H,d,J=8.3Hz), 6.96(1H,brd,J=7.6Hz), 7.11(1H,brs), 7.27-7.50(10H,m)

(3) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonylmethylethylcarbamic acid benzyl ester

To a solution of benzyl ester of 2-(4-benzyloxy-3-t-butylphenyl)-1-methylthiomethylethylcarbamic acid (1.54 g, 3.23 mmol) in THF (75 ml) and water (25 ml), oxone (5.91 g,

6.46 mmol) was added at room temperature. After stirring for 1 hour, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving the titled compound (1.59 g, 97%).

^{1}H-NMR($CDCl_3$):δ 1.38(9H,s), 2.88(3H,brs), 3.00(2H,brd,J=6.9Hz), 3.17(1H,dd,J=14.8,4.6Hz), 4.19-4.30(1H,m), 4.35-4.47(1H,m), 5.07-5.18(1H,m), 5.09(2H,s), 5.10(2H,s), 6.85(1H,d,J=8.5Hz), 6.97(1H,dd,J=8.5,1.7Hz), 7.10(1H,brs), 7.28-7.49(10H,m)

(4) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamine

A mixture of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonylmethylethylcarbamic acid benzyl ester (1.0 g, 1.96 mmol) and 20% palladium hydroxide/carbon (0.08 g) in methanol (16 ml) was stirred at room temperature in a hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.56 g, 99%).

^{1}H-NMR($CDCl_3$):δ 1.40(9H,s), 2.64(1H,dd,J=13.7,7.9Hz), 2.73(1H,dd,J=13.7,5.9Hz), 2.93-3.03(1H,m), 2.98(3H,s), 3.13(1H,dd,J=14.2,2.0), 3.61-3.74(1H,m), 6.62(1H,d,J=7.9Hz),

6.88(1H,dd,J=7.9,2.0), 7.05(1H,d,J=2.0Hz)

(5) Synthesis of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

To a solution of Z-N-Me-Val-OH (518 mg, 1.96 mmol), 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamine (0.47 g, 1.63 mmol) and CMPI (500 mg, 1.96 mmol) in THF (16 ml), TEA (0.55 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving the titled compound (0.70 g, 81%).

^{1}H-NMR($CDCl_3$):δ 0.83(3H,d,J=6.6Hz), 0.89(3H,d,J=6.3Hz), 1.38(9H,s), 2.14-2.33(1H,m), 2.64-2.97(2H,m), 2.74(3H,s), 2.91(3H,s), 3.13(1H,dd,J=14.6,4.6Hz), 3.29(1H,dd,J=14.6,6.9Hz), 3.94(1H,d,J=11.2Hz), 4.43-4.57(1H,m), 4.79(1H,brs), 5.14(2H,s), 6.40-6.84(3H,m), 7.06(1H,brs), 7.37(5H,brs).

(6) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

To a solution of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-

methanesulfonylmethylethylamide (0.65 g, 1.22 mmol) in methanol (10 ml), 10% palladium carbon (130 mg) was added and stirred in a hydrogen atmosphere at room temperature for 30 min. After filtration, the filtrate was concentrated under reduced pressure. To a solution of the thus obtained residue, Z-Phe(4-F)-OH (465 mg, 1.47 mmol) and CMPI (375 mg, 1.47 mmol) in THF (15 ml), TEA (0.41 ml, 2.93 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent:n-hexane: ethyl acetate =1:1) to give 2-((2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide (484 mg, 57%). A mixture of the above compound (424 mg, 0.609 mmol) and 10% palladium carbon (43 mg) in methanol (16 ml) was stirred at room temperature in a hydrogen atmosphere for 2 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol=15:1), giving the titled compound (239 mg, 70%).

EI-MS:563(M^+)

^{1}H-NMR($CDCl_3$):δ 0.65,0.78,0.91,0.93(6H,d,J=6.6-7.3Hz), 1.38,

1.39(9H,s), 2.22-2.40(1H,m), 2.46-3.40(6H,m), 2.66(3H,s), 2.93(3H,s), 3.60-3.83(1H,m), 3.87,4.26(1H,d,J=10.8Hz), 4.38-4.67(1H,m), 6.57-7.17,8.88(8H,m)

[0125]

Example 17

Synthesis of 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

(1) Synthesis of 3-tBu-tyrosinol

To a solution of Z-3-tBu-tyrosinol (8.2 g, 23 mmol) in methanol (250 ml), 10% palladium carbon (800 mg) was added and stirred in a hydrogen atmosphere at room temperature for 10 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the titled compound (5.1 g, 99%).

^{1}H-NMR($CDCl_3$):δ 1.40(9H,s), 2.45(1H,dd,J=8.6,13.5Hz), 2.71(1H,dd,5.3,13.5Hz), 3.0-3.2(1H,m), 3.38(1H,dd,J=7.6,10.5Hz), 3.65(1H,dd,J=3.6,10.5Hz), 6.61(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.06(1H,d,J=2.0Hz)

(2) Synthesis of (2-(benzyloxycarbonyl-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of 3-tBu-tyrosinol (1 g, 4.48 mmol), Z-N-Me-Val-OH (1.43 g, 5.4 mmol) and CMPI (1.38 g, 5.4 mmol) in THF (45 ml), TEA (2.2 ml, 15.8 mmol) was added under cooling with ice and stirred at room temperature for 13 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed

with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.9 g, 90%).

^{1}H-NMR($CDCl_3$):δ 0.84(3H,d,J=6.6Hz), 0.92(3H,d,J=6.3Hz), 2.1-2.3(1H,m), 2.5-2.8(5H,m), 3.5-3.7(2H,m), 3.9-4.2(2H,m), 5.13(2H,s), 6.2-6.4(1H,m), 6.45(1H,d,J=7.6Hz), 6.80(1H,brd,J=7.6Hz), 7.05(1H,brs), 7.36(5H,s)

(3) Synthesis of 2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of (2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (1.9 g, 4 mmol) in methanol (40 ml), 10% palladium carbon (190 mg) was added and stirred in a hydrogen atmosphere at room temperature for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (1.4 g).

To a solution of the above crude compound (1.4 g), Boc-Phe(4-F)-OH (1.4 g, 4.94 mmol) and CMPI (1.3 g, 5.09 mmol) in THF (40 ml), TEA (2 ml, 14.3 mmol) was added under cooling with ice and stirred at room temperature for 12 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and

evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.9 g, 78%).

^{1}H-NMR($CDCl_3$):δ 0.77, 0.92, and 1.02(6H,d), 1.2-1.5(18H,m), 2.2-3.1(8H,m), 3.5-3.8(2H,m), 4.0-4.3, 4.4-4.5, 4.7-4.9, and 5.2-5.4(2H,m), 6.3-7.5(8H,m)

(4) Synthesis of 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of 2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (0.5 g) in methylene chloride (2 ml), TFA (2 ml) was added under cooling with ice, stirred for 1 hour at room temperature and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (250 mg, 60%).

EI-MS:501(M^+)

^{1}H-NMR($CDCl_3$):δ 0.68, 0.79, and 0.93(6H,d,J=6.3-6.9Hz), 1.36 and 1.39(9H,s), 2.2-2.4(1H,s), 2.5-3.2(4H,m), 2.68 and 2.84(total 3H,s), 3.5-3.9(3H,m), 3.89 and 4.43(1H,d,J=10.9Hz), 4.0-4.4(1H,m), 6.5-7.1(7H,m), 6.58 and

8.41(1H,d,J=6.9-7.6Hz)

[0126]

Example 18

(2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

(1) Synthesis of (2-(2-(benzyloxycarbonylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (797 mg, 1.56 mmol) in methanol (15 ml), 10% palladium hydroxide (80 mg) was added and stirred at room temperature for 12 hours in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (400 mg, 90%).

To a solution of the above crude compound (400 mg, 1.4 mmol), Z-Val-OH (528 mg, 2.1 mmol) and CMPI (539 mg, 2.1 mmol) in THF (10 ml), TEA (0.58 ml, 4.2 mmol) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (504 mg, 69%).

^{1}H-NMR($CDCl_3$):δ 0.79(3H,d,J=6.9Hz), 0.91(3H,d,J=6.6Hz),

1.38(9H,s), 2.0-2.2(1H,m), 2.89(3H,s), 2.97(2H,d,J=6.9Hz), 3.1-3.4(2H,m), 3.94(1H,dd,J=5.6,7.9Hz), 4.4-4.6(1H,m), 5.10(2H,s), 5.1-5.2(1H,m), 5.35(1H,brs), 6.59(1H,d,J=8.3Hz), 6.5-6.7(1H,m), 6.88(1H,brd,J=8.3Hz), 7.05(1H,brs), 7.34(5H,s)

(2) Synthesis of of (1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester

To a solution of Boc-Phe(4-F)-OH (1 g, 3.53 mmol) and O,N-dimethylhydroxylamine hydrochloride (0.38 g, 3.9 mmol) in methylene chloride (17 ml), TEA (1.1 ml, 7.9 mmol) and BOP (1.64 g, 3.7 mmol) were added under cooling with ice and stirred at room temperature for 1.5 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving N-methoxy-N-methyl-2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamide (1.08 g, 94%).

To a solution of the above compound (1 g, 3.07 mmol) in ether (30 ml), lithium aluminum hydride (120 mg, 3.16 mmol) was added at -10°C and stirred at the same temperature for 10 min. The reaction mixture was mixed with 15 ml of a solution of potassium hydrogen sulfate (630 mg, 4.63 mmol). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under

reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (0.8 g, 98%).

^{1}H-NMR($CDCl_3$):δ 1.44(9H,s), 3.0-3.2(2H,m), 4.3-4.5(1H,m), 5.02(1H,brs), 7.00(2H,t,J=8.6Hz), 7.13(2H,dd,J=5.4,8.6Hz), 9.63(1H,s)

(3) Synthesis of (2-(2-(2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(2-(benzyloxycarbonylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (500 mg, 0.96 mmol) in methanol (10 ml), 10% palladium carbon (50 mg) was added and stirred in a hydrogen atmosphere at room temperature for 12 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(2-amino-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (330 mg).

To a solution of the above crude compound (330 mg, 0.86 mmol) and (1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester (275 mg, 1.03 mmol) in methanol (8 ml), acetic acid (0.07 ml, 1.22 mmol) and sodium cyanoborohydride (85 mg, 1.29 mmol) were added in that order under cooling with ice and stirred at room temperature for 30 min. The reaction mixture was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and

evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1), giving the titled compound (520 mg, 95%).

^{1}H-NMR($CDCl_3$):δ 0.68(3H,d,J=5.6Hz), 0.85(3H,d,J=6.9Hz), 1.38(9H,s), 1.41(9H,s), 1.9-2.1(1H,m), 2.4-2.9(5H,m), 2.9-3.1(2H,m), 2.99(3H,s), 3.1-3.3(2H,m), 3.8-4.0(1H,m), 4.47(1H,d, J=8.9Hz), 4.5-4.8(1H,m), 5.56(1H,brs), 6.64(1H,d,J=7.9Hz), 6.9-7.2(6H,m), 7.7-7.9(1H,m)

(4) Synthesis of (2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(2-(2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (520 mg) in methylene chloride (2 ml), TFA (2 ml) was added under cooling with ice, stirred at room temperature for 30 min. and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (400 mg, 91%).

EI-MS:535(M^+)

^{1}H-NMR($CDCl_3$):δ 0.75(3H,d,J=6.9Hz), 0.89(3H,d,J=6.9Hz),

1.39(9H,s), 2.0-2.1(1H,m), 2.3-2.5(2H,m), 2.53(1H,dd,J=3.6,11.6Hz), 2.72(1H,dd,J=4.6,13.2Hz), 2.80(1H,d,J=4.6Hz), 2.8-3.1(5H,m), 3.19(2H,d,J=5.9Hz), 4.5-4.7(1H,m),6.62(1H,d,J=7.9Hz), 6.93(1H,dd,J=2.0,7.9Hz), 6.99(2H,t,J=8.8Hz), 7.0-7.2(3H,m), 7.80(1H,d,J=8.6Hz)

[0127]

Example 19

2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone

(1) Synthesis of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropionitrile

To a solution of Z-Phe(4-benzyloxy-3-tBu)-NH_2 (4.6 g, 10 mmol) in THF (20 ml), pyridine (1.6 ml, 20 mmol) and trifluoroacetic anhydride (1.55 ml, 11 mmol) were added under cooling with ice and stirred for 4.5 days at room temperature. The reaction mixture was evaporated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:4), giving the titled compound (3.35 g, 99%).

^{1}H-NMR($CDCl_3$):δ 1.37(9H,s), 3.0(2H,m), 4.85(1H,brd), 5.03(1H,brd), 5.10(2H,s), 5.14(2H,s), 6.69(1H,d,J=8.58Hz), 7.05(1H,d,J=8.58Hz)7.2(1H,s), 7.3-7.5(10H,m)

(2) Synthesis of 2-[2-(4-benzyloxy-3-tert-butylphenyl)-1-benzyloxycarbonylaminoethyl]-6-methyl-4-pyrimidinone

A solution of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropionitrile (3.48 g, 7.85 mmol) in

saturated hydrochloric acid/ethanol (50 ml) was stirred at room temperature for 1.5 days. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was dissolved in ethanol (70 ml); into the thus obtained solution, gaseous ammonia was blown under cooling with ice, followed by stirring at room temperature for 17 hours. The resultant was concentrated under reduced pressure; the thus obtained residue was dissolved in methanol (50 ml), mixed with methyl acetoacetate (0.640 ml) and potassium hydroxide (562 mg) and stirred at room temperature for 4.5 days. The mixture was mixed with a saturated aqueous ammonium chloride solution and extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (1.76 g, 67%).

^{1}H-NMR($CDCl_3$):δ 1.39(9H,s), 2.25(3H,s), 3.09(2H,brd), 4.89(1H,brd), 5.03(2H,s), 5.07(2H,s), 5.80(1H,brd), 6.14(1H,s), 6.79(1H,d,J=8.24Hz), 6.92(1H,d,J=8.24Hz), 6.96(1H,s), 7.25-7.43(10H,m)

(3) Synthesis of 2-[1-amino-2-(3-tert-butyl-4-hydroxyphenyl)ethyl]-6-methyl-4-pyrimidinone

A suspension of 2-[2-(4-benzyloxy-3-tert-butylphenyl)-1-benzyloxycarbonylaminoethyl]-6-methyl-4-pyrimidinone (1.76 g, 3.35 mmol) and 20% palladium hydroxide/carbon (0.15 g) in methanol (30 ml) was stirred

in a hydrogen atmosphere for 16 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (824 mg, 82%).

^{1}H-NMR($CDCl_3$):δ 1.37(9H,s), 2.32(3H,s), 2.74(1H,dd,J=8.90,9.24Hz), 3.15(1H,dd,J=4.28,4.29Hz), 4.09(1H,m), 6.16(1H,s), 6.59(1H,d,J=7.92Hz), 6.83(1H,d,J=7.92Hz), 6.99(1H,s).

(4) Synthesis of 2-(1-(2-(benzyloxycarbonylmethylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone

To a solution of Z-N-Me-Val-OH (678 mg, 2.55 mmol), 2-[1-amino-2-(3-tert-butyl-4-hydroxyphenyl)ethyl]-6-methyl-4-pyrimidinone (700 mg, 2.32 mmol) and CMPI (653 mg, 2.55 mmol) in THF (20 ml), TEA (0.97 ml) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (0.77 g, 61%).

^{1}H-NMR($CDCl_3$):δ 0.79-0.90(6H,m), 1.30(9H,m), 2.2(4H,m), 2.8-3.1(5H,m), 4.3(1H,d,J=7.3), 4.97(1H,m), 5.1-5.25(2H,m), 6.18(1H,d,J=8.58), 6.41(1H,d,J=8.58Hz), 6.5-6.85(2H,m),

7.3(5H,m)

(5) Synthesis of 2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone

A mixture of 2-(1-(2-(benzyloxycarbonylmethylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (0.71 g, 1.294 mmol), 20% palladium hydroxide/carbon (0.15 g) and methanol (20 ml) was stirred in a hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving two diastereoisomers A and B of the titled compound, A (296 mg, 38%) being eluted first and then B (77 mg, 9.4%).

(A)

^{1}H-NMR($CDCl_3$):δ 0.72(3H,d,J=6.93Hz), 0.83(3H,d,J=6.93Hz), 1.34(9H,s), 1.94(1H,m), 2.28(3H,s), 2.30(3H,s), 2.77(1H,d,J=4.62Hz), 3.11(2H,m), 5.04(1H,d,J=7.59Hz), 6.14(1H,s), 6.61(1H,d,J=7.92Hz), 6.81(1H,dd,J=7.92Hz), 6.99(1H,s), 7.84(1H,d,J=6.92Hz)

(B)

^{1}H-NMR($CDCl_3$):δ 0.84(3H,d,J=6.93Hz), 0.89(3H,d,J=6.93Hz), 1.33(9H,s), 2.00(1H,m), 2.14(3H,s), 2.18(3H,s), 2.78(1H,d,J=4.95Hz), 3.11(2H,m), 5.10(1H,d,J=6.60Hz), 6.14(1H,s), 6.63(1H,d,J=7.92Hz), 6.75(1H,dd,J=7.92Hz), 6.97(1H,s), 7.81(1H,d,J=7.26Hz)

(6) Synthesis of 2-(1-(2-((2-butoxycarbonylamino-3-(4-

fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A)

To a solution of Boc-Phe(4-F)-OH (200 mg, 0.707 mmol), 2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone (A) (244 mg, 0.589 mmol) and CMPI (180 mg, 0.706 mmol) in THF (8 ml), TEA (0.25 ml, 4.7 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:n-hexane = 1:2), giving the titled compound (0.33 g, 82%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.75, 0.80 and 0.98(6H,d,J=6.6,6.9Hz), 1.34 and 1.38(9H,s), 1.4 (9H,s), 2.10(1H,m), 2.3 and 2.4(3H,s), 2.7(3H,s), 2.85(2H,m), 3.04(2H,d,J=7.01Hz), 4.12 and 4.58(1H,d,J=9.6Hz), 4.75(1H,m), 5.05(1H,m), 4.83 and 5.2(1H,brd), 5.45 and 5.6(1H,dd,J=7.4Hz), 6.2(1H,s), 6.6(1H,m), 6.77(1H,m), 7.0(5H,m)。

(7) Synthesis of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B)

To a solution of Boc-Phe(4-F)-OH (63 mg, 0.222 mmol),

2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone (B) (77 mg, 0.185 mmol) and CMPI (57 mg, 0.222 mmol) in THF (5 ml), TEA (0.08 ml, 0.573 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:n-hexane = 1:2), giving the titled compound (0.098 g, 74%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.78(6H,brd), 1.3-1.4(18H,s), 1.8(2H,brd), 2.25(3H,brd), 2.8 and 3.20(7H,brd), 4.1(2H,m), 4.4 and 4.5(1H,d,J=9.89Hz), 4.7 and 5.17(1H,brd), 5.3 and 5.58(1H,d,J=9.89Hz), 6.0 and 6.17(1H,s), 6.6(1H,brd), 6.7-7.2(8H,m)

(8) Synthesis of 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A)

To a solution of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A) (279 mg) in methylene chloride (8 ml), TFA (1.3 ml) was added under cooling with ice. The resultant mixture was stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced

pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (225 mg, 95%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.7 and 0.8(6H,dd,J=6.6 and 6.59Hz), 1.29(9H,s), 2.14 and 2.275(3H,s), 2.1-2.2(1H,m), 2.67 and 2.78(3H,s), 2.6-2.8(2H,m), 3.07(2H,m), 3.7-3.83(1H,m), 4.15 and 4.62(1H,d,J=9.87Hz), 4.98 and 5.18(1H,dd,J=6.5 and 7.6Hz), 6.02 and 6.11(1H,s), 6.55 and 6.8(2H,m), 6.92(1H,d,J=6.92Hz), 6.93-7.15(4H,m)

(9) Synthesis of 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B)

To a solution of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B) (93 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The resultant mixture was stirred at room temperature for 1.5 hours and evaporated under reduced pressure to remove the solvent; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (70 mg, 91.8%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.68, 0.78 and 0.86(6H,dd,J=6.6 and 6.27Hz), 1.3 and 1.32(9H,s), 2.21 and 2.23(3H,s), 2.2-2.4(1H,brd), 2.6 and 2.8(1H,m), 2.71-

2.91(3H,s), 3.00(3H,m), 3.77 and 3.9(1H,m), 3.97 and 4.52(1H,d,J=9.37Hz), 4.97 and 5.18(1H,m), 6.12(1H,d,J=3.3Hz), 6.5-7.2(8H,m)

[0128]

Example 20

5-(1-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

(1) Synthesis of Z-Tyr(3-tBu)-H

To a solution of Z-Tyr(3-tBu)-OMe (3.30 g, 8.57 mmol) in THF (200 ml), diisobutyl aluminum hydride (1.0 M toluene solution) (42.9 ml, 42.9 mmol) was added dropwise at -78°C over 15 min. After stirring for 1 hour, the mixture was mixed with methanol and a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with water and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (2.18 g, 72%).

NMR($CDCl_3$):δ 1.37(9H,s), 3.00-3.14(2H,m), 4.40-4.52(1H,m), 4.89(1H,brs), 5.12(2H,s), 5.22-5.32(1H,m), 6.57(1H,d,J=8.2Hz), 6.82(1H,d,J=8.2Hz),7.00(1H,s), 7.30-7.42(5H,m), 9.64(1H,s)

(2) Synthesis of 5-(1-(benzyloxycarbonylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of Z-Tyr(3-tBu)-H (2.18 g, 6.14 mmol)

in ethanol (25 ml), potassium cyanide (480 mg, 7.37 mmol), 30% ammonium carbonate (1.77 g, 18.4 mmol) and water (25 ml) were added and stirred at 60°C for 8 hours. The mixture was left for cooling and mixed with a saturated aqueous $NaHCO_3$ solution. The organic layer was extracted with ethyl acetate and washed with water and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.38 g, 53%).

^{1}H-NMR($CDCl_3$):δ 1.37(9H,s), 2.90-3.00(2H,m), 3.10-3.22(1H,m), 4.27(1H,brs), 5.06(2H,s), 5.02-5.12(1H,m), 6.07(1H,brs), 6.57(1H,d,J=8.2Hz), 6.88(1H,dd,J=2.0,8.2Hz), 7.10(1H,d,J=2.0Hz), 7.22-7.40(5H,m)

(3) Synthesis of 5-(1-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(benzyloxycarbonylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione (543 mg, 1.28 mmol) in methanol (10 ml), 10% palladium carbon (55 mg) was added and stirred at room temperature in a hydrogen atmosphere for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; to a solution of the thus obtained residue in THF (13 ml), Z-N-Me-Val-OH (509 mg, 1.92 mmol), CMPI (491 mg, 1.92 mmol) and TEA (0.535 ml, 3.84 mmol) were added under cooling with ice and stirred at room temperature for 3

hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1), giving the titled compound (365 mg, 53%).

^{1}H-NMR($CDCl_3$):δ 0.79 and 0.85(6H,d,J=6.6Hz), 2.14-2.26(1H,m), 2.60(3H,s), 2.70-2.92(2H,m), 3.89(1H,d,J=10.8Hz), 4.27(1H,brs), 4.62-4.74(2H,m), 5.14(2H,s), 6.28(1H,d,J=7.9Hz), 6.56-7.10(3H,m), 7.30-7.42(5H,m)

(4) Synthesis of 5-(1-(3-methyl-2-methylaminobutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione (363 mg, 0.675 mmol) in methanol (10 ml), 10% palladium carbon (50 mg) was added and stirred at room temperature in a hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the titled compound (261 mg, 96%).

EI-MS:404(M^+)

^{1}H-NMR(DMSO-d_6):δ 0.79 and 0.82(6H,d,J=6.3-6.6Hz), 1.31(9H,s), 1.90(3H,s), 2.74-2.84(2H,m), 4.02-4.14(1H,m), 4.17(1H,brs), 4.38-4.48(1H,m), 6.64(1H,d,J=8.2Hz), 6.82(1H,d,J=8.2Hz), 6.99(1H,s), 7.85(1H,brs)

(5) Synthesis of 5-(1-(2-(2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(3-methyl-2-methylaminobutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione (254 mg, 0.629 mmol) in THF (6 ml), Z-Phe(4-F)-OH (239 mg, 0.755 mmol), CMPI (193 mg, 0.755 mmol) and TEA (0.219 ml, 1.57 mmol) were added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (168 mg, 38%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.62,0.71,0.94 and 0.98(6H,d,J=6.0-6.6Hz), 1.34 and 1.37(9H,s), 2.26 and 2.92(3H,s), 2.24-2.42(1H,m), 2.64-3.12(4H,m), 3.84-4.32(2H,m), 4.50-4.82(2H,m), 5.02-5.12(2H,m), 5.20-5.64(1H,m), 6.21(1H,brs), 6.31(1H,brs), 6.50-6.60(2H,m), 6.86-7.14(5H,m), 7.24-7.40(5H,m), 7.50-8.00(1H,m)

(6) Synthesis of 5-(1-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(2-(2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione (157 mg, 0.223 mmol) in methanol (5 ml), 10% palladium carbon (50 mg) was added and stirred at room temperature in a hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to preparative TLC (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (83.0 mg, 65%).

FAB-MS:570($M+H^+$)

^{1}H-NMR(DMSO-d_6):(two rotamers)δ 0.48-0.84(6H,m), 1.28, 1.32 and 1.33(9H,s), 2.00-2.12(1H,m), 2.28,2.42 and 2.62(3H,s), 2.40-3.10(4H,m), 3.82-4.08(2H,m), 4.24-4.50(2H,m), 6.58-7.30(7H,m), 7.66-8.30(2H,m), 8.92-9.24(2H,m)

[0129]

Example 21

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

(1) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylcarbamic acid benzyl ester

To a solution of Z-Tyr(3-tBu)-OMe (4.0 g, 10.39 mmol) in ethanol (100 ml), hydrazine monohydrate (6.4 ml, 103.9 mmol) was added at room temperature. The mixture was stirred overnight and evaporated under reduced pressure to remove the solvent. The thus obtained residue was mixed

with ethyl orthoformate (100 ml) and p-toluenesulfonic acid monohydrate (198 mg, 1.04 mmol) at room temperature. The mixture was stirred for 1.5 hours and mixed with 1N HCl (100 ml). The mixture was stirred for 20 min., and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.34 g, 33%).

^{1}H-NMR($CDCl_3$):δ 1.32(9H,s), 3.19(2H,brs), 5.02(1H,brs), 5.05-5.16(2H,m), 5.35(2H,brs), 6.53(1H,d,J=7.9Hz), 6.75(1H,dd,J=7.9,2.0Hz), 6.85(1H,d,J=2.0Hz), 8.34(1H,s)

(2) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamine

To a solution of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylcarbamic acid benzyl ester (1.25 g, 3.16 mmol) in methanol (30 ml), 10% palladium carbon (130 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 day. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.80 g, 97%).

^{1}H-NMR($CDCl_3$):δ 1.36(9H,s), 3.02(1H,dd,J=13.8,7.9Hz),

3.18(1H,dd,J=13.8,5.6Hz), 4.47(1H,dd,J=7.9,5.6Hz), 6.57(1H,d,J=7.9Hz), 6.84(1H,dd,J=7.9,2.0Hz), 6.97(1H,d,J=2.0Hz), 8.40(1H,s)

(3) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

To a solution of Z-N-Me-Val-OH (914 mg, 3.45 mmol), 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamine (0.75 g, 2.87 mmol) and CMPI (881 mg, 3.45 mmol) in THF (30 ml), TEA (0.96 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving 2-benzyloxycarbonylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide (1.28 g, 88%).

To a solution of the above compound (1.23 g) in methanol (24 ml), 10% palladium carbon (120 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 hour. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.87 g, 96%).

^{1}H-NMR($CDCl_3$):δ 0.70(3H,d,J=6.9Hz), 0.85(3H,d,J=6.9Hz), 1.35(9H,s), 1.88-2.03(1H,m), 2.34(3H,s), 2.77(1H,d,J=4.6Hz), 3.12(1H,dd,J=14.0,8.4Hz), 3.28(1H,dd,J=14.0,5.9Hz), 5.45(1H,brs), 5.61-5.71(1H,m), 6.58(1H,d,J=8.0Hz), 6.68(1H,dd,J=8.0,2.0Hz), 6.96(1H,d,J=2.0Hz), 7.84(1H,brd,J=8.9Hz), 8.35(1H,s)

(4) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

To a solution of Z-Phe(4-F)-OH (835 mg, 2.63 mmol), 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide (0.82 g, 2.19 mmol) and CMPI (672 mg, 2.63 mmol) in THF (22 ml), TEA (0.74 ml, 5.26 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving 2-(2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)amino-N,3-dimethylbutyric acid 1-(1,3,4-oxadiazol-2-yl)-2-(3-t-butyl-4-hydroxyphenyl)ethylamide (1.31 g, 89%).

A mixture of the above compound (1.31 g, 1.95 mmol) and 10% palladium carbon (130 mg) in methanol (20 ml) was stirred at room temperature in a hydrogen atmosphere for 4

hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (752 mg, 72%).

EI-MS:539(M^+)

^{1}H-NMR($CDCl_3$):(two rotamer)δ 0.75, 0.78, 0.89, 0.92(6H,d,J=6.3-6.6Hz), 1.29,1.34(9H,s), 2.24-2.45(1H,m), 2.50-2.85(2H,m), 2.82(3H,s), 3.04-3.20(3H,m), 3.52-3.60,3.72-3.85(1H,m), 3.99,4.43(1H,d,J=10.9Hz), 5.42-5.53,5.64-5.73(1H,m), 6.42-7.18(7H,m), 8.33,8.42(1H,s), 9.62(1H,brd,J=9.2Hz)

[0130]

Example 22

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

(1) Synthesis of N-Me-Val-Tyr(3-tBu)-NH_2

To a solution of Tyr(3-tBu)-OCH_3 (1.5 g, 5.97 mmol) in MeOH (10 ml), aqueous ammonia (10 ml) was added and stirred at room temperature overnight. The mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving Tyr(3-tBu)-NH_2 (1.4 g, 99%).

To a solution of the thus obtained Tyr(3-tBu)-NH_2 (1 g, 4.23 mmol), Z-N-Me-Val-OH (1.23 g, 4.63 mmol) and CMPI (1.2

g, 4.69 mmol) in THF (20 ml), TEA (1.8 ml) was added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1), giving Z-N-Me-Val-Tyr(3-tBu)-NH_2 (1.7 g, 83%).

A mixture of the thus obtained Z-N-Me-Val-Tyr(3-tBu)-NH_2 (1.7 g), 20% palladium hydroxide/carbon (0.15 g) and methanol (30 ml) was stirred at room temperature in a hydrogen atmosphere for 1 hour. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (1.07 g, 88%).

^{1}H-NMR($CDCl_3$):δ 0.67(3H,d,J=6.27Hz), 0.80(3H,d,J=6.6Hz), 1.35(9H,s), 1.91(1H,m), 2.25(3H,s), 2.76(1H,d,J=4.62Hz), 3.00(2H,m), 4.75(1H,q,J=6.6Hz), 6.13(1H,s), 6.55(1H,s), 6.66(1H,d,J=7.92Hz), 6.89(1H,d,J=7.59Hz), 7.02(1H,s), 7.84(1H,d,J=7.91Hz)

(2) Synthesis of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2

To a solution of Boc-Phe(4-F)-OH (890 mg, 3.14 mmol), N-Me-Val-Tyr(3-tBu)-NH_2 (1 g, 2.86 mmol) and CMPI (804 mg, 3.15 mmol) in THF (20 ml), TEA (1.2 ml, 7.16 mmol) was added under cooling with ice and stirred at room

temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:n-hexane = 1:2), giving Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2 (1.5 g, 85%).

(3) Synthesis of 2-((2-tertbutoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

A solution of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2 (600 mg, 0.976 mmol) and N,N-dimethylacetamide (0.2 ml, 1.5 mmol) in dioxane (3 ml) was stirred at room temperature for 1 hour and mixed with a solution of sodium hydroxide (108 mg) and hydroxyamine hydrochloride (190 mg) in acetic acid/water (7 ml/3 ml). The mixture was stirred at room temperature for 10 min., mixed with water and filtered; a solution of the thus obtained precipitate in acetic acid/dioxane (10 ml/10 ml) was stirred at 60°C overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (474 mg, 76%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.76, 0.8, 0.86 and 0.98(6H,d,J=6.59,6.93,6.27,and 6.26Hz), 1.28 and 1.32(9H,s), 1.25 and 1.37(9H,s), 2.15(1H,m), 2.35 and 2.92(3H,s), 2.9(3H,m), 3.15(1H,d,J=6.93Hz), 4.12 and 4.49(1H,d,J=6.92Hz), 4.8(1H,m), 5.38 and 5.5(2H,m), 6.65(1H,brd), 6.9-7.2 (7H,m), 8.37(1H,brd)

(4) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

To a solution of 2-((2-tertbutoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide (440 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (370 mg, 99%).

^{1}H-NMR($CDCl_3$):(two rotamers)δ 0.75 and 0.87 (total 6H,d and dd,J=6.59 and 6.92Hz), 1.27(9H,s), 2.17(1H,m), 2.77(2H,m), 2.83(3H,s), 3.1(2H,m), 3.55(1H,m), 3.96(1H,d,J=10.89Hz), 5.7(1H,m), 6.45(1H,s), 6.59(1H,d, J=5.94Hz), 6.9(1H.brd), 8.35(1H,s), 9.5(1H,d,J=8.91Hz), 6.95(2H,t,J=8.25Hz), 7.06(2H,t,J=8.25Hz)

[0131]

Example 23

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(1) Synthesis of N-benzyloxycarbonyl-3-tBu tyrosinylthioamide

To a solution of Z-Tyr(3-tBu)-NH_2 (2.08 g, 5.62 mmol) in dioxane (70 ml), Lawesson's reagent (1.36 g, 3.37 mmol) was added and stirred at 80°C for 1 hour. The reaction mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:3), giving the titled compound (1.66 g, 77%).

^{1}H-NMR($CDCl_3$):δ 1.37(9H,s), 3.01-3.14(2H,m), 4.56-4.65(1H,m), 5.08(2H,s), 6.58(1H,d,J=7.9Hz), 6.90(1H,dd,J=7.9,1.7Hz), 7.09(1H,d,J=1.7Hz), 7.20-7.40(5H,m)

(2) Synthesis of N-benzyloxycarbonyl-2-(3-tert-butyl-4-hydroxylphenyl)-1-(thiazol-2-yl)ethylamine

To a solution of N-benzyloxycarbonyl-3-tBu tyrosinylthioamide (21.49 g, 55.67 mmol) in ethanol (300 ml), bromoacetaldehyde diethylacetal (43 ml, 278 mmol) was added, stirred at 80°C for 2 hours, further mixed with bromoacetaldehyde diethylacetal (43 ml, 278 mmol), stirred at 80°C for 4 hours, further mixed with bromoacetaldehyde diethylacetal (43 ml, 278 mmol) and stirred at 80°C for 3 hours. The mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing

solvent: ethyl acetate:n-hexane = 1:3), giving the titled compound (15.32 g, 67%).

^{1}H-NMR($CDCl_3$):δ 1.29(9H,s), 3.10-3.30(2H,m), 5.10(2H,s), 5.20-5.40(1H,m), 6.51(1H,d,J=8.3Hz), 6.74-6.78(2H,m), 7.22(1H,d,J=3.3Hz), 7.20-7.40(5H,brs), 7.76(1H,d,J=3.3Hz)

(3) Synthesis of 2-(3-tert-butyl-4-hydroxylphenyl)-1-(thiazol-2-yl)ethylamine

To a solution of N-benzyloxycarbonyl-2-(3-tert-butyl-4-hydroxylphenyl)-1-(thiazol-2-yl)ethylamine (15.28 g, 37.27 mmol) in methylene chloride (1.1 l), thioanisole (8.75 ml, 74.54 mmol) was added. To the mixture, a solution of 1.0M boron tribromide in methylene chloride (186 ml, 186.34 mmol) was added dropwise under cooling with ice and stirred for 1 hour. The reaction mixture was mixed with water and alkalinized by 2N sodium hydroxide and extracted with methylene chloride. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving the titled compound (9.46 g, 90%).

^{1}H-NMR($CDCl_3$):δ 1.36(9H,s), 2.82-3.27(2H,m), 4.51-4.56(1H,m), 6.57(1H,d,J=7.9Hz), 6.89(1H,dd,J=7.9,2.0Hz), 6.99(1H,d,J=2.0Hz), 7.27(1H,d,J=3.3Hz), 7.76(1H,d,J=3.3Hz)

(4) Synthesis of 2-(N-tert-butoxycarbonyl-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(3-tert-butyl-4-hydroxylphenyl)-1-(thiazol-2-yl)ethylamine (4.67 g, 16.64 mmol), Boc-N-Me-Val-OH (5.0 g, 21.63 mmol) and CMPI (5.53 g, 21.63 mmol) in

THF (110 ml), TEA (5.33 ml, 38.27 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (8.10 g, 100%).

^{1}H-NMR($CDCl_3$):δ 0.75-0.97(6H,m), 1.29(6H,s), 1.31(3H,s), 1.41(3H,s), 1.48(6H,s), 2.10-2.35(1H,m), 2.71(1.5H,s), 2.73(1.5H,s), 3.10-3.30(2H,m), 3.90-4.10(1H,m), 5.50-5.70(1H,m), 6.58(1H,d,J=7.9Hz), 6.70-6.90(2H,m), 7.20(1H,d,J=3.0Hz), 7.74-7.76(1H,m)

(5) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(N-tert-butoxycarbonyl-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (8.03 g, 16.42 mmol) in methylene chloride (80 ml), TFA (40 ml) was added and stirred at room temperature for 30 min. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue

was subjected to silica gel column chromatography (developing solvent: acetone:hexane = 1:2), giving two diastereoisomers A and B of the titled compound, A (2.37 g, 37%) being eluted first and then B (2.17 g, 34%).

(A)

^{1}H-NMR($CDCl_3$):δ 0.65(3H,d,J=6.9Hz), 0.82(3H,d,J=6.9Hz), 1.33(9H,s), 1.85-2.00(1H,m), 2.32(3H,s), 2.75(1H,d,J=4.6Hz), 3.09-3.37(2H,m), 5.63-5.71(1H,m), 6.61(1H,d,J=7.9Hz), 6.87-6.92(2H,m), 7.22(1H,d,J=3.0Hz), 7.77(1H,d,J=3.3Hz)

(B)

^{1}H-NMR($CDCl_3$):δ 0.84(3H,d,J=6.9Hz), 0.92(3H,d,J=6.9Hz), 1.33(9H,s), 1.95-2.15(1H,m), 2.11(3H,s), 2.68(1H,d,J=5.0Hz), 3.12-3.39(2H,m), 5.60-5.69(1H,m), 6.59(1H,d,J=8.2Hz), 6.87(1H,dd,J=7.9,2.0Hz), 6.93(1H,d,J=2.0Hz), 7.22(1H,d,J=3.3Hz), 7.77(1H,d,J=3.3Hz)

(6) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (1.00 g, 2.57 mmol), Boc-Phe(4-F)-OH (947 mg, 3.34 mmol) and CMPI (853 mg, 3.34 mmol) in THF (17 ml), TEA (0.82 ml, 5.91 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the

solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (1.55 g, 92%).

^{1}H-NMR($CDCl_3$):δ 0.76(3H,d,J=6.6Hz), 0.86(2H,d,J=6.6Hz), 0.97(1H,d,J=6.6Hz), 1.26(3H,s), 1.29(6H,s), 1.37(6H,s), 1.40(3H,s), 2.15-2.40(1H,m), 2.70-3.50(4H,m), 2.78(3H,s), 4.17(0.3H,d,J=10.2Hz), 4.49(0.7H,d,J=11.2Hz), 4.70-4.85(1H,m), 5.25-5.80(1H,m), 6.58(1H,d,J=7.9Hz), 6.75-7.30(6H,m), 7.21(0.7H,d,J=3.3Hz), 7.23(0.3H,d,J=3.3Hz), 7.74(0.3H,d,J=3.3Hz), 7.77(0.7H,d,J=3.3Hz)

(7) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (1.00 g, 2.57 mmol), Boc-Phe(4-F)-OH (947 mg, 3.34 mmol) and CMPI (853 mg, 3.34 mmol) in THF (17 ml), TEA (0.82 ml, 5.91 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (1.54 g, 92%).

^{1}H-NMR($CDCl_3$):δ 0.57(1H,d,J=6.6Hz), 0.62(1H,d,J=6.9Hz), 0.78(4H,d,J=6.3Hz), 1.33(9H,s), 1.36(9H,s), 2.10-2.30(1H,m), 2.60-3.70(4H,m), 2.82(1.8H,s), 2.85(1.2H,s), 3.99(0.3H,d,J=10.6Hz), 4.51(0.7H,d,J=10.9Hz), 4.70-4.90(1H,m), 5.20-5.60(1H,m), 6.59-7.21(7H,m), 7.20(1H,d,J=3.3Hz), 7.71(1H,d,J=3.3Hz)

(8) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (1.49 g, 2.28 mmol) in methylene chloride (20 ml), TFA (10 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (430 mg).

EI-MS:554(M^+)

^{1}H-NMR($CDCl_3$):δ 0.75(2.3H,d,J=6.9Hz), 0.80(0.7H,d,J=6.6Hz), 0.90-0.92(0.7H,m), 0.93(2.3H,d,J=6.6Hz), 1.24(7H,s), 1.30(2H,s), 2.25-2.65(1H,m), 2.70-3.40(4H,m), 2.79(2.4H,s), 2.85(0.6H,s), 3.50-3.60(0.8H,m), 3.75-3.90(0.2H,m),

3.97(0.8H,d,J=10.9Hz), 4.51(0.2H,d,J=10.6Hz), 5.45-5.60(0.2H,m), 5.65-5.80(0.8H,m), 6.55-7.20(7H,m), 7.23(1H,d,J=3.3Hz), 7.76(1H,d,J=3.3Hz)

(9) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (1.48 g, 2.26 mmol) in methylene chloride (20 ml), TFA (10 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (587 mg).

EI-MS:554(M^+)

^{1}H-NMR($CDCl_3$):δ 0.72(1.5H,d,J=6.9Hz), 0.786(1.5H,d,J=6.3Hz), 0.793(1.5H,d,J=6.6Hz), 0.88(1.5H,d,J=6.3Hz), 1.24(5.4H,s), 1.33(3.6H,s), 2.15-2.40(1H,m), 2.40-3.35(4H,m), 2.75(1.8H,s), 2.87(1.2H,s), 3.55-3.85(1H,m), 3.86(0.6H,d,J=10.9Hz), 4.56(0.4H,d,J=10.9Hz), 5.50-5.65(1H,m), 6.45-7.15(7H,m), 7.17-7.20(1H,m), 7.23(1H,d,J=3.3Hz), 7.76(1H,d,J=3.0Hz)

[0132]

Example 24

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide

To a solution of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH_2 (400 mg, 0.651 mmol) in methylene chloride (6.5 ml), dimethylformamide dimethylacetal (0.26 ml, 1.954 mmol) was added at room temperature. The mixture was stirred for 30 min. and evaporated to remove the solvent under reduced pressure. To a solution of the thus obtained residue in dioxane (6.5 ml), acetic acid (2 ml) and hydrazine monohydrate (48 µl, 0.977 mmol) were added at room temperature. The mixture was stirred for 40 min., mixed with water and filtered to collect the precipitated solid. The thus obtained solid was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving 2-((2-t-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide (384 mg, 93%).

To a solution of the above compound (421 mg) in methylene chloride (3 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 30 min., mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated brine,

dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (175 mg, 49%).

EI-MS:538(M^+)

^{1}H-NMR($CDCl_3$):δ 0.72,0.87,0.73-0.80(6H,d,J=6.3-6.6Hz), 1.22, 1.25(9H,s), 2.24-2.41(1H,m), 2.50-3.30(4H,m), 2.78, 2.87(3H,s), 3.47-3.58, 3.79-3.88(1H,m), 4.00,4.39(1H,brd,J=10.6Hz), 5.29-5.38,5.40-5.50(1H,m), 6.41-7.11(7H,m), 7.52,9.33(1H,brd,J=8.3Hz), 8.02,8.10(1H,s)

[0133]

Example 25

2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(1) Synthesis of 2-tert-butoxycarbonylamino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of Boc-Val-OH (890 mg, 4.09 mmol), 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (1.03 g, 3.73 mmol) and CMPI (653 mg, 1.05 mmol) in THF (10 ml), TEA (1 ml) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under

reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.88 g, 99%).

^{1}H-NMR($CDCl_3$):δ 0.79 and 0.89(6H,d,J=6.93Hz), 1.29 and 1.31(9H,s), 1.42 and 1.44(9H,s), 2.15(1H,brd), 3.23(2H,m), 3.89(1H,m), 5.0(1H,brd), 5.4(0.7H, brd), 5.57(1H,q,J=6.93 and 5.92Hz), 6.56(1H,q,J=4.62 and 4.29Hz), 6.8(3H,brd), 7.21(1H,m), 7.75(1H,t,J=2.07 and 3.3Hz)

(2) Synthesis of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (1.7 g) in methylene chloride (14 ml), TFA (6 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol:ethyl acetate = 20:1:2), giving two diastereoisomers A and B of the titled compound, A (700 mg) being eluted first and then B (650 mg, 99%).

(A)

^{1}H-NMR($CDCl_3$-CD_3OD):δ 0.89(6H,brd), 1.28(9H,s), 2.15(1H,m), 3.18-3.7(3H,m), 5.48(1H,brd), 6.6(1H,brd), 6.8(2H,brd), 7.27(1H,s), 7.7(1H,s)

(B)

^{1}H-NMR($CDCl_3$-CD_3OD):δ 0.72(6H,d,J=6.27Hz), 1.31(9H,s), 1.92(1H,brd), 3.04(2H,brd), 3.28(1H,dd,J=5.28 and 5.6Hz),

5.55(1H,m), 6.62(1H,d,J=7.92Hz), 6.86(1H,brd), 6.97(1H,s), 7.28(1H,s), 7.68(1H,d,J=2.64Hz)

(3) Synthesis of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (600 mg, 1.59 mmol) and (1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester (640 mg, 2.39 mmol) in MeOH (10 ml), $NaBH_3CN$ (200 mg, 3.1 mmol) was added under cooling with ice and stirred at room temperature for one hour. The mixture was evaporated under reduced pressure, mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (935 mg, 93%).

^{1}H-NMR($CDCl_3$):δ 0.75 and 0.83(6H,d,J=6.93 and 6.59Hz), 1.36(9H,s), 1.42(9H,s), 2.46(2H,brd), 2.66(2H,brd), 2.73(1H,d, J=4.61Hz), 2.81(1H,d, J=7.26Hz), 3.20(2H,d,J=6.26Hz), 3.6(2H,m), 3.8(1H,brd), 4.7(1H,brd), 5.6(1H,q,J=6.93 and 5.94Hz), 6.61(1H,d,J=7.92Hz), 6.77(1H,s), 6.85(1H,d,J=7.92Hz), 6.9-7.21(8H,m), 7.66(1H,d,J=2.97Hz)

(4) Synthesis of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-

butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (600 mg, 1.59 mmol) and 1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester (640 mg, 2.39 mmol) in MeOH (10 ml), $NaBH_3CN$ (200 mg, 3.1 mmol) was added under cooling with ice and stirred at room temperature for one hour. The mixture was evaporated under reduced pressure, mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (950 mg, 95%).

^{1}H-NMR($CDCl_3$):δ 0.83 and 0.87(6H,d,J=6.93 and 6.92Hz), 1.34(9H,s), 1.41(9H,s), 2.00(1H,brd), 2.31(2H,brd), 2.6-2.81(3H,brd), 2.81(1H,d, J=7.26Hz), 3.20(2H,m), 3.6(2H,m), 3.8(1H,brd), 4.58(1H,brd), 4.83(1H,brd), 5.59(2H,q,J=6.93Hz), 6.60(1H,d,J=7.92Hz), 6.81(1H,d,J=7.91Hz), 6.88(1H,s), 6.9-7.21(8H,m), 7.74(1H,d,J=2.29Hz)

(5) Synthesis of 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (300

mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (180 mg, 71%).

^{1}H-NMR(DMSO-d_6):δ 0.78 and 0.88(6H,d,J=3.3 and 5.6Hz), 1.28(9H,s), 1.90(1H,brd), 2.6(1H,m), 2.7-3.0(3H,brd), 3.1(2H,m), 3.4(1H,brd), 5.29(1H,q,J=5.93 and 8.58Hz), 6.69(1H,d,J=7.92Hz), 6.86(1H,d,J=7.59Hz), 6.95(1H,s), 7.2(4H,m), 7.62(1H,d,J=2.97Hz), 7.77(1H,d,J=3.3Hz)

(6) Synthesis of 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (300 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (193 mg, 76%).

^{1}H-NMR(DMSO-d_6):δ 0.61(6H,q,J=6.6 and 12.54Hz), 1.3(9H,s), 1.72(1H,s), 2.7-3.0(4H,brd), 3.16(1H,s), 3.28(1H,m), 3.5(1H,brd), 5.37(1H,m), 6.65(1H,d,J=8.25Hz),

6.85(1H,d,J=10.89Hz), 7.0(1H,s), 7.2(4H,m),
7.68(1H,d,J=2.97Hz), 7.81(1H,d,J=3.3Hz)

[0134]

Test Example 1

Motilin receptor binding test

A motilin receptor binding test was conducted in the following manner [Vantrappen et al., Regul. Peptides, 15, 143 (1986)]. The duodenum was extracted from a slaughtered rabbit, had the mucous membrane separated and homogenized in 50 mM Tris buffer to prepare a protein sample. The protein sample was incubated together with ^{125}I motilin 25 pM and thereafter the radioactivity bound to the protein was measured. Specific binding was defined as the difference between the radioactivity in the case of adding a great excess amount of motilin (10^{-7} M) and that in the case of no adding. The activity of the compound was expressed by IC_{50} (in nM), as the concentration sufficient to reduce the specific binding by 50%. Result is shown in Table B-1.

[0135]

Test Example 2

Action on the contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit

The action on the motilin-induced contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit was investigated by the following method. A duodenum specimen (5 x 15 mm) extracted from a slaughtered rabbit was suspended in an organ bath (10 ml) such that the longitudinal muscle would run vertically; the bath was

filled with a Krebs solution kept at 28°C. A mixed gas (95% O_2 and 5% CO_2) was continuously bubbled into the Krebs solution and the contraction of the duodenum specimen was recorded isotonically (with a 1-g load) via an isotonic transducer (ME-3407, ME Commercial, Tokyo, Japan). The degree of contraction was expressed in relative values, with the contraction by acetylcholine at a dose of 10^{-4} M being taken as 100%. The activity of the compound was calculated as pA_2 value indicating its effect on the dose-dependent muscle contraction by the motilin put into the organ bath. The result is shown in Table B-1.

[0136]

[Table 9]

Table B-1

Example No.	Motilin receptor binding test, IC_{50} (nM)	Contraction suppressing test, pA_2
1	0.89	8.8
2	0.71	8.7
3	1.5	8.7
4	1.6	8.3
8	0.35	9.5
9	1.0	9.0
12	0.52	9.3
14	0.70	9.3
15	0.82	8.5
16	0.41	9.4
17	0.70	9.1
19	2.2	8.7
21	0.27	9.8
22	0.52	8.3
23	0.67	9.3
24	0.94	9.1

[0137]

[Advantages]

The compounds of the present invention function as a motilin receptor antagonist and are useful as medicines including therapeutics of irritable bowel syndrome.

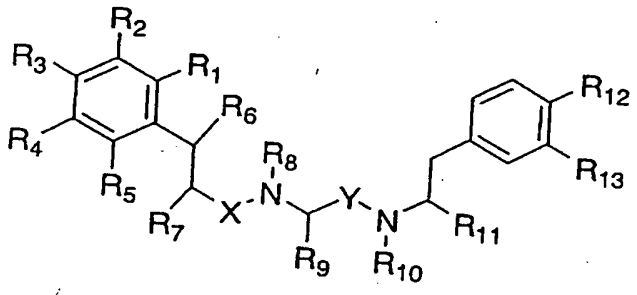
[Name of Document] Abstract

[Abstract]

[Problem] The present invention has as its object providing halogen-substituted benzene derivatives that function as a motilin receptor antagonist and which are useful as medicines.

[Means for Solving] The invention provides compounds of Formula (1):

[Chemical Formula 1]



(1)

wherein:

R_1, R_2, R_3, R_4 and R_5 are hydrogen, halogen, etc. and at least one of R_1, R_2, R_3, R_4 and R_5 is halogen;

R_6 is alkyl, etc.;

R_7 is amino, etc.;

R_8 is methyl, etc.;

R_9 is alkyl, etc.;

R_{10} is methyl, etc.;

R_{11} is alkyl, etc.;

R_{12} is hydroxy, etc.;

R_{13} is alkyl, etc.:

X is carbonyl, etc.;

Y is carbonyl, etc.;

or a hydrate or pharmaceutically acceptable salt thereof.

[Advantages] Compounds of the above Formula (1) function as a motilin receptor antagonist and are useful as medicines.

[Selected Drawing] None